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Testicular cancer: diagnostic and surgical strategies to improve outcome

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Contents

Introduction

General Introduction

Testicular germ cell tumors (TGCTs) account for only 1% of all malignancies and are the most common solid tumors in men aged between 20-35 years[1,2]. The historic pathway in the diagnostic and combined treatment of testicular cancer e.g. nonseminomatous germ cell tumors (NSTGCTs or nonseminoma), represents one of the greatest success stories in the treatment of cancer in the 20th century. This journey to cure in NSTGCTs is marked by the discovery of the effectiveness of cisplatin based combination chemotherapy in disseminated NSTGCT followed by, if indicated, adjuvant surgery. The integration of cancer care involving different medical and surgical specialties has led to significant advances in the multimodal treatment of TGCTs.

Men with testicular cancer (TC) nowadays have one of the highest survival rates of any solid organ malignancy with a cure rate of 90-95 %[1,2]. The fundamental elements of the successful multimodality testicular cancer treatment include improved staging techniques, cisplatin based combination chemotherapy, aggressive surgical approach in case of residual disease and/or recurrent disease. Close follow-up after treatment with serum tumor marker checks and repeated CT-scan assures early detection of recurrent disease resulting in excellent second line treatment options for optimal oncologic outcome.

Still in the 21th century additional progress is made in the insight of the disease, the molecular biology of TC, the diagnostic, staging and (combined) treatment of especially NSTGCTs, as well as psychosocial support.

Incidence

Testicular cancer is a rare malignancy, generally occurring in Caucasian young men. However, TGCTs are the most prevalent type of malignancy in men aged between 20 and 35 years. For NSTGCTs the incidence peak is at 25 years of age and for seminomatous germ cell tumors (or seminoma) 10 years later at 35 years. Beyond 40 years old, incidence rates decline more quickly for NSTGCTs compared to seminomas and therefore in older men more often seminomas are diagnosed. Geographic variation in testicular cancer incidence rates exists with the highest incidence in Scandinavian, Western European countries, New Zealand and North America and the lowest in Africa and Asia[3,4]. The incidence is rising in the United States and in parts of Western Europe[4-6]. In the United States in 2016 an estimated 8700 men were diagnosed with TC[2] and the incidence has been increasing from 5.7 per 100.000 in 1992 to 6.8 per 100.000 in 2009[3]. In the Netherlands, 782 men were diagnosed with testicular cancer in 2017 of which 323 men had NSTGCTs.

Geographic clustering of testicular cancer is present in the northern part of the Netherlands with areas with some stable founder populations[6]. While the incidence has increased since the nineties in the Netherlands (Figure 1), numbers on survival since diagnosis are continuously improving (Figure 2)[1]. Ten year survival in the eighties was about 66% compared to 97% in 2010[1].

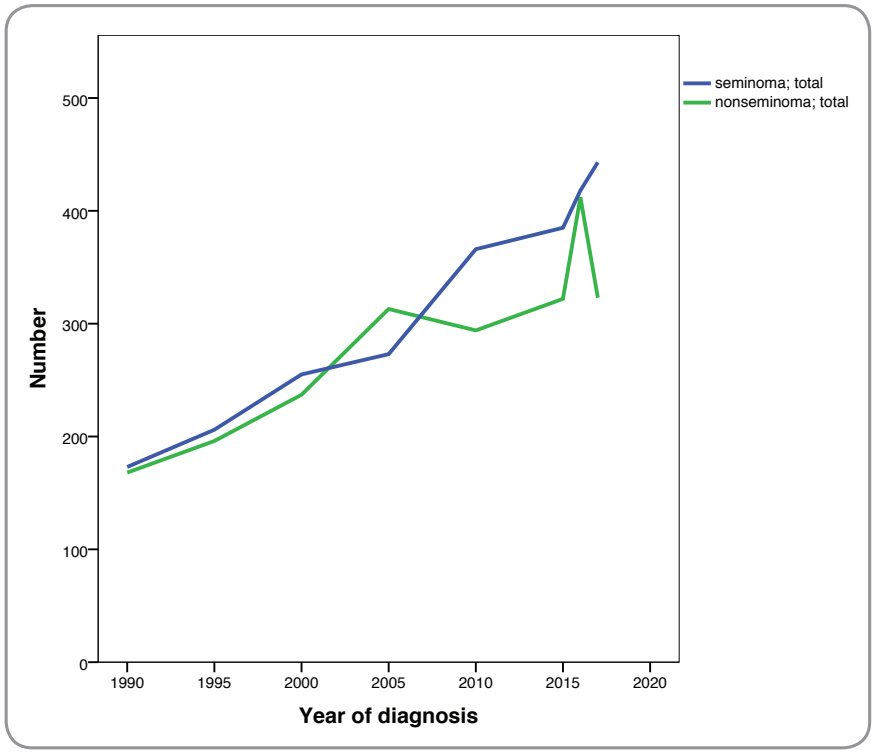

Figure 1.
Incidence of testicular cancer (seminoma vs nonseminoma) in the Netherlands during the period 1990-2017[1].

Etiology

The etiology of testicular germ cell tumors is still poorly understood. Various pre-existing medical conditions such as a family history of testicular cancer, testicular atrophy, infertility, prior testicular cancer, family history of testicular cancer brother or father, have been associated in literature with the development of TGCTs[7,8].
The only established risk factor for the development of a testicular tumor is still cryptorchidism, first mentioned by LeComte in 1851. At the UMCG, 5.2% of all

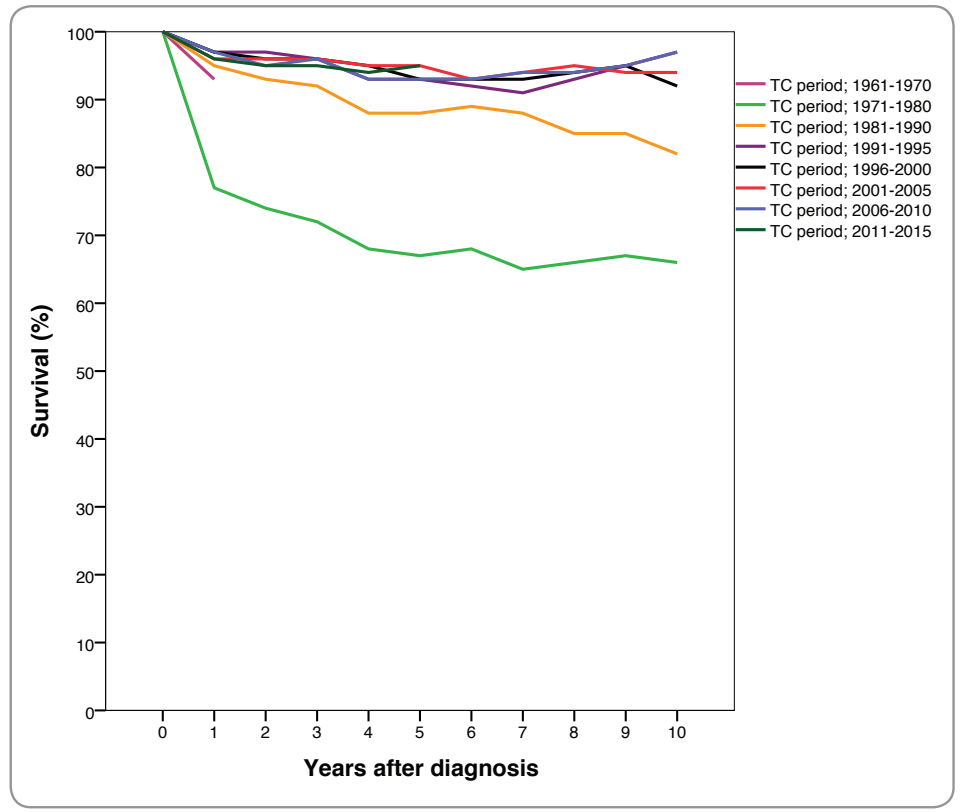

Figure 2.
Survival of testicular cancer in the Netherlands during different periods[1].

diagnosed TGCTs developed in an undescended testicle[9]. In a meta-analysis the estimated relative risk of 4.8 was found of TGCT among men with prior cryptorchidism[10]. It remains unclear whether cryptorchidism predisposes to the development of testicular cancer or cryptorchidism and TGCT share common risk factors. Also, the increasing incidence rate for TGCT cannot be explained by cryptorchidism since the proportion of testicular cancer patients with cryptorchidism remains constant.
Two other risk factors are also associated with the development of TGCTs. Pre- and postnatal exposure to endocrine disrupting chemicals is a risk factor[11]. There is also increasing evidence that certain chromosomal areas are involved in an increased risk of TGCTs being formed and so far 44 risk loci have already been identified[12-14].

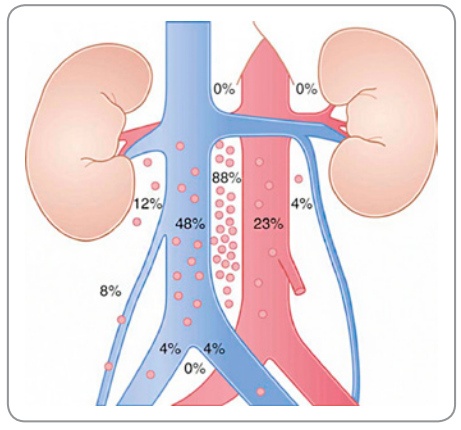

Figure 3a.
Pattern of early retroperitoneal lymph node involvement from right-sided testicular tumors[16].

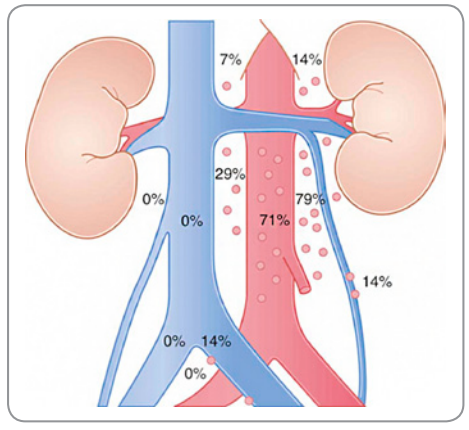

Figure 3b.
Pattern of early retroperitoneal lymph node involvement from left-sided testicular tumors[16].

Clinical Presentation and Dissemination

Testicular cancer mainly spreads via the lymphatic and circulatory systems. Testicles descend embryologically via the retroperitoneal route and inguinal canal into the scrotum. Testicular lymphatic drainage is consistent and follows the general scheme of vertical drainage with lateral flow from right to left. Along this dissemination route regional metastases from TGCT first arise in the retroperitoneal lymph nodes. First lymph node stations to be affected are the lumbar lymph nodes, and from there, at a higher supradiaphragmatic level, lymphogenous spread advances via the thoracic duct to the mediastinum and supraclavicular lymph nodes[15]. Right-sided TGCT tends to metastasize to the interaortocaval lymph nodes, and a left-sided TGCT to the paraaortal lymph nodes (Figure 3)[16].

Haematogenic, dissemination can take place directly to the lungs via vascular invasion in the testicle, or indirectly to the lungs via the retroperitoneal lymph nodes, cisterna chyli and the thoracic duct to the subclavian vein. Haematogenous dissemination is predominantly to the lungs and less frequent and in a later disease stage dissemination occurs to liver, cerebrum or the skeleton. These non-pulmonary visceral metastases represent nearly 10% of metastatic sites of advanced germ cell tumors and are associated with poor prognosis[16].

Histology

Testicular germ cell tumors account for 90% of primary tumors of the testes, with a small percentage being sex cord/stromal tumors. Majority of germ cell tumors arise from progression of an intratubular malignant germ cell that has the morphologic and immunohistochemical features of a seminoma cell. This precursor lesion is also called "germ cell neoplasia in situ (GCNIS)" of the testis according to the WHO recommendations[17].
Testicular germ cell tumors are a heterogeneous group of neoplasms exhibiting diverse histopathologic features and can be classified as seminomatous germ cell tumors (seminoma) and nonseminomatous germ cell tumors (nonseminoma). Although mixed germ cell tumors contain more than one germ cell component they are classified and treated as nonseminomas according to the World Health Organization (WHO) classification system since nonseminomatous components are present and the dissemination pattern is equal to nonseminomas. The classification of the WHO is most often used and is shown in Table 1[17].

Main subtypes of nonseminoma germ cell tumors (NSTGCTs) include yolk sac tumors, embryonal carcinoma, choriocarcinomas and teratomas. Embryonal carcinoma is the most poorly differentiated tumor component; no specific differentiation direction is recognizable. In nonseminoma, embryonal carcinoma cells are the principal metastatic cells and tumor components are associated with production of alpha-fetoprotein (AFP) and/or betachoriongonadotropin (B-HCG). Yolk sac tumor and choriocarcinoma resemble fetal membranes and placental tissue, respectively. Yolk sac tumor in adults occurs often in combination with other elements. Metastases from yolk sac tumors occur via both lymphatic and haematogenous routes. Distant metastases most often affect lungs and liver. Yolk sac tumor is associated with AFP production. Pure choriocarcinoma has the highest potential for organ confined metastases and is associated with high levels of B-HCG and concordantly with a very poor prognosis[18]. It metastasizes diffusely via the blood stream, often skipping the retroperitoneum. Often nonseminoma consist of a mix with other different components and elevated levels of B-HCG and AFP can often be found. Testicular teratoma is a subtype of NSTGCT and can be divided histologically into mature and immature teratoma. In adults the presence of mature and immature teratoma features have a metastatic potential and may undergo malignant transformation also into non-germ cell cancers such as sarcoma. Serum tumor markers, AFP and/or B-HCG, are normal in patients with pure teratoma. Surgical removal of teratoma containing lesions is the fundamental part of the treatment, since teratomas are poorly responsive to both chemotherapy and radiotherapy.

Table 1.
Histological classification of testicular tumors

Germ cell tumors derived from germ cell neoplasia in situ

- Non-invasive germ cell neoplasia
  - Germ cell neoplasia in situ
  - Specific forms of intratubular germ cell neoplasia
- Tumors of a single histological type (pure forms)
  - Seminoma
    - Variant: Seminoma with syncytiotrophoblastic cells
    - Partially regressed tumor showing seminoma with scar
  - Spermatocytic seminoma
    - Variant: Spermatocytic seminoma with sarcomatous component
  - Nonseminomatous germ cell tumors
    - Embryonal carcinoma
    - Yolk sac tumor, postpubertal-type
    - Trophoblastic tumors
      - Choriocarcinoma
      - Non-choriocarcinomatous trophoblastic tumors
      - Placental site trophoblastic tumor
      - Epithelioid trophoblastic tumor
      - Cystic trophoblastic tumor
    - Teratoma, postpubertal-type
    - Teratoma with somatic-type malignancy
- Nonseminomatous germ cell tumors of more than one histological type
  - Mixed germ cell tumors
- Germ cell tumors of unknown type
  - Regressed germ cell tumors

Germ cell tumors unrelated to germ cell neoplasia in situ

- Spermatocytic tumor
- Teratoma, prepubertal-type
- Mixed teratoma and yolk sac tumor, prepubertal-type
- Yolk sac tumor, prepubertal-type

Table 1. Continued

Sex cord-stromal tumors

- Pure tumors
  - Leydig cell tumor
  - Sertoli cell tumor
  - Granulosa cell tumor
  - Tumors in the fibroma-thecoma group
- Mixed and unclassified sex cord stromal tumor
  - Mixed sex cord-stromal tumor
  - Unclassified sex cord-stromal tumor
- Tumor containing both germ cell and sex cord-stromal elements
  - Gonadoblastoma
  - Unclassified

Miscellaneous tumors of the testis

- Ovarian epithelial-type tumors
- Juvenile xanthogranuloma
- Haemangioma

Haematolymphoid tumors

- Diffuse large B-cell lymphoma
- Follicular lymphoma, NOS
- Extranodal NK/T-cell lymphoma, nasal-type
- Plasmacytoma
- Myeloid sarcoma
- Rosai-Dorfman disease

Tumors of collecting duct and rete testis

- Adenoma
- Adenocarcinoma

**A summarized version based on fourth edition of the World Health Organization (WHO) classification of urogenital tumours (WHO "blue book"), published in 2016[17].*

Clinical Presentation

A wide variation in clinical presentation exists. In most cases patients with testicular cancer present with a change in the testicle (e.g. a painful or painless lump or enlargement of the testicle), however other causes of scrotal swelling are more common, such as trauma/sports injuries, epididymitis, orchitis, torsion of the testicle or cellulitis. However rare, an intratesticular mass should be considered malignant until proven otherwise. Thorough physical investigation and an ultrasound of the scrotum should be performed to rule out cancer. Several studies have shown that TC can also present itself with other nonspecific symptoms and extra testicular manifestation, often caused by metastatic disease, such as back pain, chough with hemoptysis and/or gynaecomastia as a result of elevated B-HCG[19,20].

TC is rare and many young men do not know of the existence of this disease[21]. Lack of knowledge about TC and a feel of shame might affect delay in diagnosis. Delay in the treatment of TC is correlated to more advanced disease requiring intensive treatment and increasing morbidity and mortality[21,22].

Delay in TC may also be due to general practitioners (GP) who have the important role of recognizing the relevant symptoms and providing further evaluation and access to specialist care when necessary. However, in an average general practice in the Netherlands, a GP will see a patient with TC once every 10 years.

Awareness of the existence of testicular cancer and early symptoms among patients and general practitioners is crucial in reducing delay in diagnosis and treatment and therefore optimising survival rates.

Diagnosis

Young men presenting with testicular complaints should always be taken seriously with a thorough medical history. Physical examination includes first palpation of the scrotum to differentiate between an intratesticular or an extratesticular mass and is followed by a complete examination of the abdomen, chest, mammae and supraclavicular lymph nodes. In patients presenting with palpable abnormality or scrotal swelling, ultrasonography can detect, locate, and characterize both intratesticular and extratesticular masses and other abnormalities. Vascular perfusion can be easily assessed using color and spectral Doppler analysis. In most cases of scrotal disease, the combination of medical history, physical examination, and information obtained with ultrasonography and testicular tumor markers (AFP, B-HCG and LDH) is sufficient for diagnostic decision making. NSTGCTs present ultrasonographically as heterogeneous and cystic masses with irregular margins[23]. Echogenic foci within the mass may be seen, however, the underlying testicular parenchyma demonstrates an inhomogeneous appearance rather than a regular echotexture[23]. Sensitivity of ultrasound is almost 100% in detecting a testicular malignancy[24]. Testicular microcalcifications are incidentally found on ultrasonography and are only seen in about 5% of males between the age of 17 and 35[25]. Although current literature does not provide any proof that testicular microcalcifications can be regarded as a premalignant condition, microlithiasis has been associated with testicular neoplasms[26].

Testicular tumor markers are essential in the diagnosis, staging, prognosis, treatment response and follow up of TGCTs. The level of tumor markers in the serum if elevated at diagnosis provides information on treatment response and is helpful in monitoring relapse during follow up[27]. Two types of glycoproteins, being alpha fetoprotein and betachorionicgonadotropin may be produced by TGCTs. Serum B-HCG may be slightly increased in patients with a seminoma. With regard to NSTGCTs, B-HCG can be markedly elevated with pure choriocarcinomas. In combination with embryonal carcinoma and mixed TGCTs there is a moderate elevation[27]. Limited elevations of B-HCG can also be seen in 20% of patients with stage I seminoma and up to 30%–50% of disseminated seminoma[28].

In all patients with TC, the serum lactate dehydrogenase (LDH) level may be increased. LDH is a cellular enzyme produced by muscle, liver, kidney, and brain that catalyzes the interconversion of lactate and pyruvate. LDH has relatively low specificity for TGCTs. Therefore elevations of LDH must be taken in the context of the two other testicular tumor markers, AFP and B-HCG, and staging studies. An elevated serum LDH level may be the sole biochemical abnormality in 10% of patients with persistent or recurrent NSTGCTs[28,29].

Radical inguinal orchiectomy is required with high ligation of the spermatic cord, gonadal and lymph vessels in patients with a suspicious testicular mass and abnormal biomarker results. If there is a clinically suspicious mass in combination with normal laboratory results, explorative surgery including biopsies with frozen section histology is performed. Core needle biopsy for histology or fine needle aspiration (FNA) for cytology is seldom indicated.

Staging

After diagnosis of testicular cancer, the patient is staged with a computed tomography (CT) scan of the abdomen and chest to establish the presence of lymphogenic, lung and/or haematogenic metastases. The supraclavicular nodes are assessed by physical examination or CT-scan[30]. Magnetic resonance imaging (MRI) produces similar results to CT. MRI can be helpful when CT or ultrasonography are inconclusive, and when CT is contraindicated due to contrast allergy. There is no evidence to support the use of 18 fluorodeoxyglucose-PET (FDG-PET) in the staging of testicular cancer[31,32].

After cisplatin based combination chemotherapy for disseminated TGCTs, patients are restaged with abdominal and chest CT for the presence or absence of residual

Table 2.
TNM classification for testicular cancer (UICC, 2017, 8th edn.[34-36])

T	Primary Tumor
pTX	Primary tumor cannot be assessed, no radical orchiectomy has been performed
pT0	No evidence of primary tumor (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1*	Tumor limited to testis and epididymis without vascular/lymphatic invasion: tumor may invade tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion
N	Regional Lymph Nodes (clinical, cN)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
pN	Regional Lymph Nodes (pathologic, pN)
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M	Distant Metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non regional lymph node(s) or lung metastasis
M1b	Distant metastasis other than non regional lymph nodes and lung
S	Serum Tumor Markers
SX	Serum marker studies not available or not performed
S0	Serum marker study levels within normal limits

Table 2. Continued

	LDH (U/l)	B-HCG (mIU/mL)	AFP (ng/mL)
S1	<1.5 x N¶ and	<5,000 and	<1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	<10 x N or	<50,000 or	<10,000

** AJCC subdivides T1 by T1a and T1b depending on size ≤3 cm or <3 cm in greatest dimension. ¶ N indicates the upper limit of normal for the LDH assay.*
Abbreviations: LDH = lactate dehydrogenase; B-HCG = betachoriongonadotropin; AFP = alpha-fetoprotein.

disease. FDG-PET/CT has some value in the post chemotherapy management of seminoma patients with large volume residual disease[31,32]. In patients with NSTGCT treated with chemotherapy 18FDG-PET has a low sensitivity and specificity and is unable to give a clear additional clinical benefit to the standard restaging CT-scan and serum tumor markers, in prediction of tumor viability in residual masses[31-33].

In Europe the most commonly used staging system for the primary tumor is the TNM staging system, which was developed by the American Joint Committee on Cancer (AJCC) and adopted by the Union for International Cancer Control (UICC) (Table 2)[34-36].

Also, the Royal Marsden staging classification is a widely used clinical staging system (Table 3)[37]. At the University Medical Center Groningen (UMCG), patients with TGCTs are staged according to the Royal Marsden Hospital Classification. Patients with stage I disease have no clinical, radiological or biochemical evidence of metastases. In case of involvement of infradiaphragmatic or supradiaphragmatic lymph nodes it is classified as stage II or III. When distant metastases to lung, liver, brain, or bone are present, this is called stage IV[37].

In 1997, in order to achieve uniformity, the International Germ Cell Cancer Collaborative Group (IGCCCG), defined a prognostic factor-based staging system (Table 4) for metastatic testicular tumors based on identification of clinically independent adverse factors such as primary tumor site, histology, tumor markers after orchiectomy before start of chemotherapy, and extent of disease[38]. Based on the different prognostic factors, three groups are produced: 'good', 'intermediate' or 'poor' prognosis[38]. A treatment plan is drawn up on the basis of this subgroup classification.

Table 3.
Royal Marsden staging classification of testicular germ cell tumors[37]

Stage	Description
I	Confined to the testis and peritesticular tissue
IM	Rising concentrations of serum tumor markers without evidence of metastatic disease
II	Abdominal nodal metastasis
• IIA	<2 cm
• IIB	2–5 cm
• IIC	<5 cm
III	Supradiaphragmatic nodal metastasis
• M	Mediastinal
• N	Supraclavicular, cervical or axillary
• O	No abdominal node metastasis (Node stage as described for stage II above)
IV	Disseminated disease
• Lung	
◦ *L1	<3 metastases
◦ *L2	≥3 metastases, ≤2 cm diameter
◦ *L3	≥3 metastases, one or more <2 cm diameter
H+	Liver metastasis
Br+	Brain metastasis
Bo+	Bone metastasis

Treatment

Stage I NSTGCT Disease

Approximately 50% of patients with NSTGCT are classified as clinical stage I disease, which indicates that the tumor is confined to the testis and no evidence of metastases are found. Standard treatment options for patients with clinical stage I disease include radical inguinal orchiectomy, followed by close surveillance ("wait and see" policy) or retroperitoneal lymph node dissection (RPLND) or chemotherapy (1-2 cycles of bleomycin, etopiside, and cisplatin (BEP)). Each of these three treatment modalities is supported by literature[39]. Historically,

Table 4.
IGCCCG prognostic classification for metastatic germ cell cancer[38]

	Nonseminoma	Seminoma
Good prognosis	Testis/retroperitoneal primary • **and** No non-pulmonary visceral metastases • **and** AFP <1000 ng/ml • **and** B-HCG <1000 ng/ml • **and** LDH <1.5xN*	Any primary site • **and** No non-pulmonary visceral metastases • **and** Normal AFP, any B-HCG, any LDH
Intermediate prognosis	Testis/retroperitoneal primary • **and** No non-pulmonary visceral metastases • **and** 1000 ≤AFP ≤10.000 ng/ml • **or** 1000 ≤B-HCG ≤10.000 ng/ml • or 1.5xN ≤LDH ≤10xN	Any primary site • **and** Non-pulmonary visceral metastases • **and** Normal AFP, any B-HCG, any LDH
Poor prognosis	Mediastinal primary • **and** Non-pulmonary visceral metastases • **or** AFP >10.000 ng/ml • **or** B-HCG >10.000 ng/ml • **or** LDH >10xN	No patients classified as poor prognosis

treatment consisted of primary RPLND and this remains an important strategy but less frequently used in current practice. At the UMCG, the wait and see policy has been applied since 1982 in patients with stage I disease[40]. However, up to 30 % of these patients will have unrecognized subclinical metastases and will relapse with surveillance alone, usually in the first two years after orchiectomy[41]. This also implies that for 70% of patients with stage I disease potentially unnecessary treatment is avoided. Although the surveillance policy is mainly recommended in Europe even in 'high risk' patients and primary RPLND mainly is a standard approach in the USA, a shift in treatment patterns away from aggressive surgical management to surveillance has been seen[39]. Despite this shift, no difference in overall survival has been detected between the treatment modalities, surveillance, surgery, or chemotherapy in stage I NSTGCTs (Figure 4)[39].

Treatment can also be adopted to prognostic factors for metastatic disease, in other words a risk adapted approach. The best predictor regarding risk of relapse is the presence of vascular invasion (VI) in the primary tumor[42]. Other predictors are proliferation rate, as well as the percentage of embryonal carcinoma in relation to the tumor volume[43].

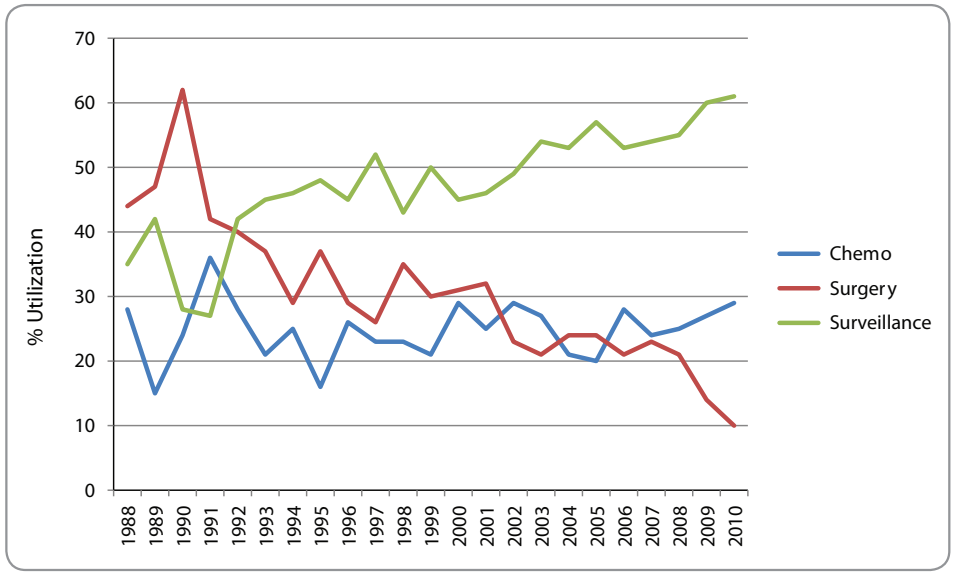

Figure 4.
Primary management following radical orchiectomy for patients presenting with stage I NSTGCT across the years[39].

For patients with stage I NSTGCT in the high risk group, treatment with RPLND or one or two cycles of chemotherapy (BEP) has been utilized and achieves relapse rates of less than 5 %[44,45]. An advantage can be a reduced follow up regimen and reduced radiation burden due to CT scans. However, the disadvantage of RPLND (operative morbidity, loss of ejaculatory function) or chemotherapy (toxicity, late effects of chemotherapy) must be taken into account. Surveillance offers the lowest treatment related morbidity. At the UMCG, the wait and see policy is also applied in both high and low risk patients. This may be a demonstration of the shift toward patient centered care with a trade-off between disease control and health related quality of life and survivorship[46]. Ultimately, the best approach depends on a number of factors, such as risk factors for disease relapse, accurate clinical staging, discussion of treatment options and the joint decision making between patient and oncological health care provider.

Advanced Disease

Metastatic germ cell tumors account for a total of 40% of all diagnosed patients. Treatment for patients with stage II-IV metastasized NSTGCTs comprises of chemotherapy in accordance with the prognostic factor classification[38]. Combination chemotherapy consists of bleomycin, etoposide, and cisplatin (BEP). In the good prognosis group, it was shown that patients with NSTGCTs require three cycles of BEP, whereas for patients in the intermediate- and poor prognosis group, four cycles of BEP remains the standard treatment[30,38,47].

Surgery after combination chemotherapy in advanced NSTGCT

After completion of chemotherapy, patients with advanced NSTGCT, undergo restaging procedures. When no residual disease is shown, or residual masses are smaller than 1 cm, tumor markers have normalized, there is no indication for surgical resection and a wait and see policy can be implemented. However when residual disease is identified, patients should undergo postchemotherapy resection of residual retroperitoneal tumor masses (RRRTM). In patients with metastatic NSTGCT who have normal tumor markers after chemotherapy, surgical resection of residual disease is indicated, to evaluate tumor histology, since it is not possible to predict the histology of the residual tumor. Teratoma has to be removed since it lacks the chemosensitivity to cisplatin based combination chemotherapy and consequently it may continue to grow or de-differentiate into a non-germ cell malignancy. The key therapeutic option is complete resection with histology being the second most important prognostic factor. Histological examination of these residual masses shows that the mass consists of necrosis in 45% of cases, mature (or immature) teratoma in 40%, viable germ cell cancer in 10%, and non-germ cell malignancy in the remaining 5%[48]. When only necrosis and or fibrosis is encountered in the RRTM, prognosis is excellent and no further treatment is required. However when viable germ cell cancer is present, prognosis is less favourable and depending on factors such as the initial IGCCCG classification, the volume of residual viable germ cell cancer and the completeness of resection, 2 additional courses of chemotherapy VIP (etoposide, ifosfamide, cisplatin) are indicated. Prior research at the UMCG has shown that the presence of teratoma elements in the primary tumor predicts residual mature teratoma[49]. Clinical significance of mature teratoma in the residual tumor is still poorly understood and the natural course remains unpredictable. It is known however in literature that growing mature teratoma or secondary non-germ cell malignancies (e.g. sarcoma) may occur. Radical surgery in most cases is the only curative treatment option for these non-germ cell malignancies.

Follow up in TGCTs

Optimal follow up is critical to the care of TGCT patients for recurrences and/or short- and long-term treatment related morbidity.
Patients are followed by regular outpatients visits, during which physical examination, serum tumor marker analysis[50], and radiological examinations are performed. In most commonly used schedules, patients will visit a medical specialist

multiple times over a period of 10 years. Some advocate even lifelong follow up as late relapses have been recorded[51].
A subset of patients will harbor unresected disease or develop a recurrence in the retroperitoneum in the postchemotherapy surgical setting after prior retroperitoneal lymph node dissection (RPLND) or resection of a residual retroperitoneal tumor mass (RRRTM)[52,53]. Options for treatment are second line chemotherapy with the TIP regimen (paclitaxel, ifosfamide, cisplatin), surgery or both modalities of treatment. Since these relapses of the retroperitoneum tend to be chemoresistent, a selection of patients with anatomically well defined retroperitoneal disease require surgery with a curative intent. These redo surgeries are accompanied by significant morbidity and risks and can be technically challenging procedures because of postchemotherapy desmoplastic reaction and annihilated surgical tissue planes and dense adhesions due to prior surgery[52]. All of these factors increase the possibility of an adjunctive procedure such as a nephrectomy, resection of visceral structures and vascular surgery.
Post-treatment late effects and long-term toxicity have emerged as an important issue for TGCT survivors. Examples of late effects are secondary non-germ cell malignancies and cardiovascular disease, which represent the most severe and potentially life threatening effects of testicular cancer treatment. Follow up of testicular cancer survivors should include recommendations for maintaining a healthy lifestyle to reduce the risk of serious long-term and late effects of treatment, e.g. cardiovascular disease.

Aims and research questions of this thesis

The research on patients with testicular cancer within national and international collaborations during the past forty years at the University Medical Center Groningen focused on epidemiological, pathological, genetical, surgical, urological, medical, endocrinological, cardiovascular, sexual and psychosocial aspects of testicular cancer as a disease and the combined modality treatment in testicular cancer, and ultimately formed the basis for the enormous acquired knowledge of this rare disease (see 'Historical overview of testicular cancer treatment at the UMCG'). Research has led to new insights and treatment strategies, resulting in an increased cure rate of 20% in the sixties to almost 90% today, less treatment related short- and long-term morbidity and a better understanding of the disease by basic scientists, medical specialists, patients, partners, families and caregivers.
Have the various oncological care-givers, psycho-oncologists and basic scientists not already finished raising and answering the testicular research questions? The answer is "no, they have not". Testicular cancer research is still needed, since newly raised questions need to be answered. The aim of this thesis is to further improve knowledge and expertise with respect to testicular cancer diagnosis, treatment and long-term outcome to benefit the patient with testicular cancer and his family. At the end of the nineties all 'surgical research questions' seemed to be answered. Since treatment of testicular cancer is characterized by excellent survival rates, attention is nowadays focused on fine tuning different aspects in testicular cancer treatment. Further refinements in the management of testicular cancer, are focused on reducing toxicity and morbidity of treatment regimens and improving cosmetic results related to surgery.

The research performed and reported in this thesis addresses various aspects concerning the treatment of nonseminomatous germ cell tumors (NSTGCT). With the introduction of minimal invasive surgical procedures in cancer treatment, the question was raised if this technique could also be applied in the surgical treatment of testicular cancer.
This thesis focused further on delay in the diagnosis of testicular tumors and aspects of new treatment strategies in staging and surgical treatment of testicular cancer. The following questions were raised:

Surgical Research Questions

- Are men and physicians aware of testicular cancer?
- Is it possible to use volumetric CT analysis to measure the therapeutic response of retroperitoneal lymph nodes in testicular cancer after chemotherapy?
- What is the short-term outcome of laparoscopic resection of testicular residual retroperitoneal tumor after systemic treatment?
- What is de short- and long-term outcome of (hand-assisted) laparoscopic resection of testicular residual retroperitoneal tumor after systemic treatment?
- Are there new surgical strategies to resect retroperitoneal tumor recurrence?

In the various chapters in this thesis are the previous research questions answered, followed by a summary and future perspectives.

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Delay in Diagnosis of Testicular Cancer; A Need for Awareness Programs

Abstract

Background

Aim: to gain insight into patient and doctor delay in testicular cancer (TC) and factors associated with delay.

Methods

Sixty of the 66 eligible men; median age 26 (range 17-45) years, diagnosed with TC at the University Medical Center Groningen completed a questionnaire on patients' delay: interval from symptom onset to first consultation with a general practitioner (GP) and doctors' delay: interval between GP and specialist visit.

Results

Median patient reported delay was 30 (range 1-365) days. Patient delay and TC tumor stage were associated (p = .01). Lower educated men and men embarrassed about their scrotal change reported longer patient delay (r = -.25, r = .79 respectively). Age, marital status, TC awareness, warning signals, nor perceived limitations were associated with patient delay. Median patient reported time from GP to specialist (doctors' delay) was 7 (range 0-240) days. Referral time and disease stage were associated (p = .04). Six patients never reported a scrotal change. Of the 54 patients reporting a testicular change, 29 (54%) patients were initially 'misdiagnosed', leading to a median doctors' delay of 14 (1-240) days, which was longer (p <.001) than in the 25 (46%) patients whose GP suspected TC (median doctors' delay 1 (0-7 days).

Conclusions

High variation in patients' and doctors' delay was found. Most important risk variables for longer patient delay were embarrassment and lower education. Most important risk variable in GP's was 'misdiagnosis'. TC awareness programs for men and physicians are required to decrease delay in the diagnosis of TC and improve disease free survival.

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Introduction

Current survival rates in testicular cancer (TC) are high[1]. However, delay in TC diagnosis relates to more advanced disease requiring intensive chemotherapy treatment with increased morbidity and decreased survival[2-5]. Delay in TC can be patient related or doctor related.

Until now, only a few, mainly qualitative studies, have explored delay in men diagnosed with TC[6-8]. These studies suggest that delay seems associated with men's unawareness of the existence of TC and of warning signals such as a testicular lump or scrotal pain. Such signals may be appraised as a temporary annoyance and not serious enough to seek medical help. Also, TC affects an intimate organ in a group characterized by issues of masculinity, attractiveness, sexual functioning and other aspects of young adulthood[9]. Embarrassment to discuss testicular abnormalities could lead to delay in help-seeking behavior[10-12]. Additionally, TC mainly affects young men in a period of life when men generally do not perceive themselves as susceptible to serious disease and therefore are less likely to interpret symptoms as threatening[12]. Perceived susceptibility and perceived threat, which varies between individuals and is associated with engagement in health-related behaviors, are essential constructs in the Health Belief Model (HBM)[13].

Besides age, in cancer literature, educational level and marital status seem to be related to patient delay[14,15]. However in TC, to our knowledge only one study included education as a possible factor and reported no effect on delay and another study included marital status and found also no effect on delay[16,17].

Delay in TC diagnosis can also be physician related, according to Andersen's model of total patient delay[18]. In an average general practice in the Netherlands, a general practitioner (GP) will see a patient with TC once every 10 years. GPs have the important role of recognizing the relevant symptoms and providing further access to specialist care, if necessary. According to the Dutch TC guideline, patients suspected of having TC by their GP must be seen and treated by a specialist within three days[19]. In the UK exists the 'two-week wait rules', indicating that a patient must be seen within two weeks when urologic cancer is suspected[20]. TC diagnosis is complex because other causes than TC of scrotal swelling are more common (e.g. epididymitis, sports injuries) and patients may report complaints not associated with the testicle but caused by metastatic disease, such as fatigue, back pain and/or gynaecomastia[10,21-23]. The very low prevalence of TC, unfamiliarity with the disease, and the diversity and ambiguity of warning signals increases the chance of misdiagnosis and of delay in secondary referrals[10,24,25].

This study aims first to gain insight into length of patients' and doctors' delay in TC diagnosis, and second to examine factors associated with the delay in TC diagnosis. Knowledge thus gained may provide recommendations for a timely diagnosis of TC.

2

Materials and Methods

Procedure and Patients

All patients diagnosed with TC of all stages at the Department of Surgical Oncology, University Medical Center Groningen (UMCG), the Netherlands were approached to participate in this single-center, observational, quantitative study over a 3-year period. To be eligible, patients must have had sufficient command of the Dutch language. Patients with a psychiatric condition were excluded. All patients were staged with the biomarkers lactodehydrogenase (LDH), alpha-fetoprotein (AFP) and betachoriongonadotropin (B-HCG), and with spiral computed tomography (CT) of the chest, abdomen and pelvis according to the Royal Marsden Classification and the International Germ Cell Cancer Collaborative Group (IGCCCG). Stages range from stage 1 (no evidence of metastasis) to stage 4 (evidence of extralymfatic metastasis)[26,27]. Patients with stage I disease were treated with a so called Wait and See policy. Patients with TC stages II-IV were treated with orchiectomy, cisplatin based combination chemotherapy, and if indicated adjuvant surgery, eg. resection of residual disease. The surgical oncologist informed the patients diagnosed with TC on the goal of the quality of life study and provided an envelope with a questionnaire and informed consent form. Patients signed the written informed consent form, and returned the questionnaires in a prepaid return envelope. Approval of the study was granted by the UMCG Medical Ethics Review Committee (UMCG IRB 2000/027). The study was supported by a grant from The Dutch Cancer Society (RUG 99-2130).

Instruments

A questionnaire was developed including questions on diagnostic time path and possible predictors of delay that synthesized knowledge about TC disease-specific characteristics, Andersen's model of total patient delay, the Health Belief Model (HBM), and the interview study of Gascoigne et al[10,13,18,28].

Diagnostic Time Path

TCPs were asked to indicate the date on which they first detected symptoms and the date of the first consultation with a general practitioner (GP) (patient delay), and the date on which they consulted a GP for the symptoms they experienced and for the first time visited a medical specialist for these symptoms (doctor delay).

Factors Associated with Delay

Patients completed questions on the following socio-demographic and illness characteristics: age, educational level, marital status, and stage of disease. Highest educational level completed was measured on a seven-point scale, ranging from primary school only (1), lower vocational degree (2), middle secondary degree (3), middle vocational degree (4), high secondary degree (5), high vocational degree (6), to university degree (7). Stage of disease (I through IV) was checked in the patient's medical record.

Further, patients filled in questions about TC awareness ('heard of TC'), warning signals (i.e. change in a testicle, such as a swelling or a hard lump; scrotal pain; interpretation of testicular change as cancer), limitations in daily functioning ("did you experience limitations in daily functioning because of the symptoms?"), and embarrassment about a testicular change (range 1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). Limitations in daily functioning were seen as relevant since a perceived barrier could enhance the likelihood of health-promoting behavior, such as consulting a doctor (HBM). Also, patients were asked to indicate the diagnosis made or suspected by the GP or physician they first consulted and to what disease or cause they attributed their testicular change.

Statistical Analyses

Statistical analyses were performed with SPSS 18.0 (SPSS Inc., USA). Descriptive analyses were used to calculate means, medians, frequencies and percentages. To examine factors associated with delay, Mann-Whitney U tests and Pearson's correlations were conducted, as appropriate. Correlations with a coefficient <0.30 were considered weak, between 0.30-0.50 moderately strong, and >0.50 strong[29].

Results

Participants

Sixty-one of the 66 eligible patients returned the questionnaire (response = 91%). One patient returned an almost blank questionnaire. Therefore, analyses were performed on 60 patients. Median age was 26 (range 17-45) years. Of the patients, 3.4% completed primary school only, 8.5% completed low vocational degree, 18.6% middle secondary degree, 33.9% middle vocational degree, 16.9% high secondary degree, 15.3% high vocational degree, and 3.4% had completed university.

Fifty-two percent did not have a partner. Seventy-seven percent of the patients was diagnosed with extensive disease (stages II-IV) (Table 1).

Diagnostic Time Path

Patient Delay (Figure 1). Median patient reported delay was 30 (range 1-365) days. Almost all TCPs (57/60, 95%) consulted the GP, the vast majority (n = 49, (86%)) for a testicular change. Three patients initially reported other symptoms, and eventually a testicular change. The remaining five patients never perceived a scrotal change. Two patients immediately consulted an urologist because of a testicular change and the last patient visited the Emergency Department with complaints other than testicular and was diagnosed with a thrombosis of the lower limb. Altogether, 6 of the 60 patients (10%) never noticed a scrotal change. Of the 54 patients noticing a testicular change, 29 patients (54%) answered that they did not consider a specific disease for the testicular change and 16 patients (30%) attributed their symptoms to diseases or causes, such as inguinal hernia (n = 3), inflammation/epididymitis (n = 5), sports injury (n = 1), Crohn's disease (n = 2), gastritis (n = 1), hydrocele (n = 1), puberty (n = 2), or dental problem (n = 1) (9 answers missing).

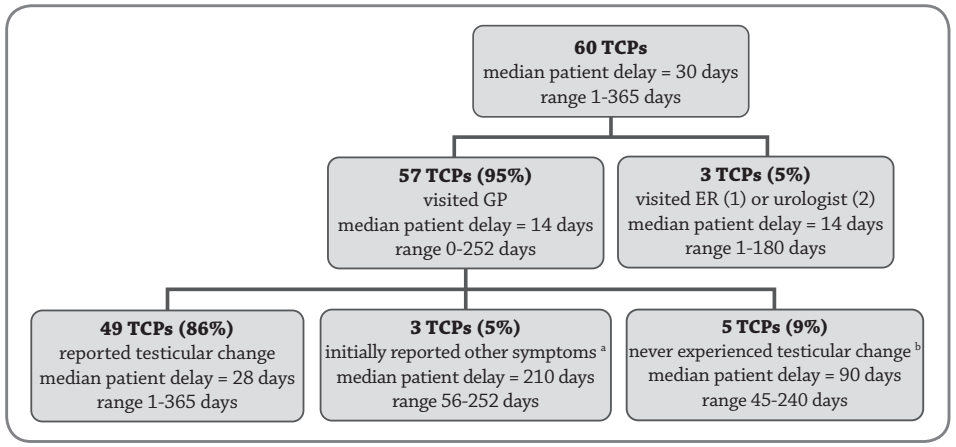

Figure 1.
Diagnostic time path: patient delay.
[a] *TCPs initially reported back pain (n = 2), abdominal pain (n = 1).*
[b] *TCPs reported: stress (n = 1), pulmonary symptoms (n = 2), stomach ache (n = 1), or fatigue (n = 1).*

Doctor Delay (Figure 2). Median patient remembered GPs' referral time to a specialist was 7 (range 0-240) days. Of the 49 patients who consulted their GP because of a scrotal change at their first visit, 20 patients (41%) were referred for further examination to and seen by a specialist within 3 (median 1; range 0-3) days, 15 patients (31%) were referred and seen between 5 and 14 days, and the remaining 14 patients (28%) between 17 and 240 (median 51) days.
Of the two patients who went to a urologist, one was diagnosed with TC at day 5 and the second was first diagnosed and treated for epididymitis and diagnosed with TC at day 42. The patient who went to the Emergency Department was diagnosed with TC at day 3.

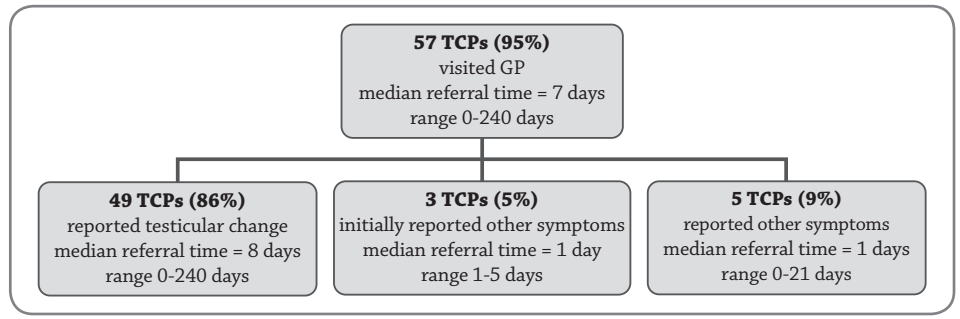

Figure 2.
Diagnostic time path: doctor delay.

Variables Associated with Patient Delay

Variables possibly associated with patient delay are summarized in Table 1, and the details are summarized for patient characteristics, TC awareness, warning signals, limitations in daily functioning and embarrassment.

Patient Characteristics. No significant effect on patient delay was found of age and partnership status (r = .05 and Z = .18, respectively). Educational level was negatively but weakly correlated with patient delay (r = -.25, p = .03). A significant moderately strong positive association between disease stage and patient delay was found (r = .33, p <.01).

TC Awareness. Median patient delay was not significantly different between those who did (n = 31) and those who did not (n = 29) know of TC before diagnosis, nor in the total group (60 men) or in the group experiencing a testicular change (54 men). As in the total group, 48% of the men experiencing a testicular change indicated they knew of TC before diagnosis. Twelve (39%) of the 31 patients

Table 1.
Descriptives and effect of patient related factors on patient delay and doctor related factors on doctor delay

Variables (n = 60)			N (%)	Delay (days) median (range)	Correlation R/ Z - statistic	P-value
Patient	Median age at diagnosis (in years)		26 (17–45)		-.05[a]	.35
	Educational level[c]		4 (1–7)		-.25[a]	.03
	Partner	Yes	29 (48)	30 (2–365)	.18[b]	.54
		No	31 (52)	39 (1–252)		
	Stage of disease		2 (1–4)		.33[a]	.01
		Stage I	14 (23)	30 (2–365)		
		Stage II	28 (47)	14 (1–120)		
		Stage III	4 (7)	136 (30–240)		
		Stage IV	14 (23)	106 (1–252)		
Awareness	'Heard of TC' before diagnosis (n = 60)	Yes	31 (52)	30 (1–240)	.02[b]	.98
		No	29 (48)	30 (1–365)		
Warning signals	Change in a testicle as a symptom (n = 60)	Yes	54 (88)	30 (1–365)	.20[b]	.86
		No	6 (12)	67 (1–240)		
	Pain in a testicle as a symptom (n = 54)	Yes	38 (70)	29 (1–210)	-.46[b]	.65
		No	16 (30)	27.5 (1–365)		
	Association of change with cancer (n = 54)	Yes	9 (17)	21 (2–56)	-1.27[b]	.21
		No[d]	45 (83)	35 (1–365)		

Table 1. Continued

Variables (n = 60)			N (%)	Delay (days) median (range)	Correlation R/ Z - statistic	P-value
Limitations	Limitations in daily living (n = 60)	Yes	25 (42)	39 (1–252)	1.13[b]	.26
		No	35 (58)			
Embarrassment	Feeling embarrassed scrotal change (n = 54)	not at all (1)	17 (38)		.79[a]	<.001
		somewhat (2)	19 (42)			
		quite a bit (3)	6 (13)			
		very much (4)	3 (7)			
		Missing data	9			
Doctor	Patients consulting with testicular change (n = 54)	TC suspected	25 (46)	1 (0–7)	5.32[b]	<0.001
		First otherwise diagnosed	29 (54)	14 (1–240)		
	Patients consulting without testicular change (n = 6)	TC suspected	3 (50)	2 (0–3)	1.96[b]	.05
		First otherwise diagnosed	3 (50)	21 (14–135)		
	Stage of disease				.28 [a]	.04

[a] *Pearson correlation coefficient.*
[b] *Mann-Whitney U test.*
[c] *Highest educational level completed: primary school only (1), low vocational degree (2), middle secondary degree (3), middle vocational degree (4), high secondary degree (5), high vocational degree (6), university degree (7).*

reporting they knew of TC before their diagnosis had heard of Lance Armstrong's fight against TC.

Warning Signals. No significant effect on patient delay was found of the experience of a scrotal change, painfulness of the testicle, and the association of scrotal change with TC. Of the 26 patients (48%) who experienced a scrotal change and who knew of the existence of TC, 17 patients (65%) did not associate their scrotal change with TC.

Limitations. No significant differences were found in patient delay between patients who reported limitations in daily functioning because of symptoms (n = 25) and those who experienced no limitations (n = 35).

Embarrassment. Of the 54 patients who reported a scrotal change, 9 did not provide an answer to the question on embarrassment. Of the remaining 45, 17 (38%) did not feel at all embarrassed about the change in their testicle, 19 (42%) felt somewhat embarrassed, 6 (14%) felt quite a bit embarrassed, and 3 patients (7%) felt very embarrassed. The relationship between embarrassment and patient delay was significant and strong ($r = .79$, $p < .001$).

Variables Associated with Doctor Delay

Variables possibly associated with doctor delay are summarized in Table 1, and the details are summarized for scrotal change and pain, and misdiagnosis.

Scrotal Change and Pain. The difference in patient reported doctor delay between the 54 TCPs who reported a scrotal change and the six patients who never experienced a scrotal change was not significant ($Z = -.99$, $p = .34$). Patient reported pain in a testicle had no effect on doctor referral time ($Z = 1.5$, $p = .13$).

Misdiagnosis. Doctor delay was significantly longer in the 29 patients (54%) who were first misdiagnosed (median = 14, range 1-240 days) than in the 25 patients (46%) immediately suspected of having TC (median 1; range 0-7 days). These 29 patients were first diagnosed by their GP with back pain (3), epididymitis (9), hydrocele (5), trauma (2), inguinal hernia (1), appendicitis (1), urinary tract infection (1), gynaecomastia (1), and in some cases no diagnoses was made (6). GP's suspected TC in three of the six patients not reporting a scrotal change resulting in a significantly shorter referral time than in the three patients not complaining of a scrotal change and who were first otherwise diagnosed (hyperventilation, asthma, gastritis).

Finally, a positive significant weak correlation was found between doctor's delay and disease stage ($r = .28$, $p < .05$).

Discussion

A wide time range in patient and doctor delay was found. Patient and doctor delay were associated with more advanced disease. Delay was longer in patients who had completed a low level education and in those feeling embarrassed about a scrotal change. Longer delay in GPs was associated with initially misdiagnosing the patient.

Median patient delay in TC diagnosis in this study was 30 days, which was shorter in comparison to two studies from the eighties, but similar to a more recent study[2,17,30]. The present study displayed a wide range in patient delay. However, in contrast to the previous studies, none of the men in the present study waited longer than one year before consulting a GP.

The current study showed that educational level was significantly related to patient delay, which was in contrast to a previous study[16]. Lower educated men reported a longer patient delay. Age was not related to patient delay. It may well be that the oldest TCPs (45 years), who were still relatively young, did not feel susceptible to disease yet. Marital status was not related to patient delay, conform a previous study[17].

Present study results show that TC awareness seems not sufficient as adequate health behaviour. Approximately half of the respondents had heard of TC before diagnosis but length of patient delay was comparable to that in patients who did not have TC awareness. In addition, neither the interpretation of a testicular change as possibly being related to cancer nor specific symptoms such as scrotal change and pain, possibly causing limitations in daily living, seemed to urge men to seek help more promptly. However, "having heard of TC" seems not to be the same as having "actual TC knowledge"[8]. Having detailed and correct information of the cause and symptoms of TC can heighten men's disease awareness and possibly lead to an earlier GP visit.

Literature remains indistinct about the exact relevance of testicular self-examination (TSE)[31-33]. The present study seems to support the view that men do not fail to detect scrotal changes but fail to act adequately upon it[32]. Nevertheless, researchers have pleaded for health education in young men to increase TC knowledge and raise awareness of the normal shape and feel of testicles, because it may encourage men to act upon scrotal changes more adequately[2,4,33,34]. Embarrassment about the scrotal change was strongly associated with longer patient delay ($p < 0.001$), endorsing previous suggestions that feeling embarrassed about a testicular abnormality acts as a barrier to taking action[10,11].

Median GP referral time in patients with testicular complaints in the current study was 7 days, which was shorter than in two other studies reporting 10 and 14 days respectively, and conform a third study[2,28,36]. In the present study, two-fifth of patients with a testicular change were referred within 3 days, conform the Dutch TC guideline, and almost three-quarter were referred within two weeks, conform the current UK guideline[19,20]. Although Dutch GP's refer a large percentage of young men reporting a scrotal change adequately, misdiagnosis seems to be a risk factor for longer doctor delay in the diagnostic process. TC is a rare disease, but GPs should always bear TC in mind, in particular when adolescents and young adult men present with inguinal or scrotal complaints, or lower back pain.

Findings of the present study accentuate the difficulty of the TC diagnostic process, and underlines the responsibility of GPs in this process. A recent English study showed that the positive predictive value for testicular cancer following a GP's referral for a scrotal abnormality conform the two weeks rule is only 17%[37]. In the Netherlands, GPs refer patients with a scrotal mass to a radiologist for an ultrasonography. If the ultrasound is abnormal and TC is suspected, a patient is immediately referred to a surgical oncologist or urologist to confirm the diagnosis and if needed, for treatment.

The present study showed that both longer patient delay and doctor delay were significantly associated with more advanced disease, which is in concordance with other studies[4,24]. Advanced disease requires more intensive cancer treatment and is associated with increased treatment related morbidity, decreased disease free survival and increased costs.

A few limitations of the present study should be mentioned. First, methodological concerns regarding the concept of delay exist and a standardized definition is lacking. Definitions used in this study have proven operational earlier[25]. Second, patient-centered studies measuring delay are susceptible to recall bias. In particular patients reporting longer time intervals could have had difficulty remembering the exact time span. Third, to our knowledge, a validated questionnaire on this subject is not available, and thus a questionnaire incorporating information regarding TC and health behavior was developed for the present study. Fourth, the number of respondents in some subgroups is small which may affect the statistical power.

Conclusion

High variation in patient and doctor delay was found. Patient and doctor delay were associated with more advanced disease requiring a more intensive cancer treatment. Health care providers who aim to develop education programs to increase TC awareness in young men should take into account that men who feel embarrassed about scrotal changes and lower educated men may benefit most from their programs. To prevent misdiagnoses, education programs for GPs should focus on increasing GPs knowledge of TC and on their awareness that TC may be the underlying illness in adolescent and young adult men who present with a scrotal change or with symptoms possibly considered vague. Further policy recommendations are continuous medical education of GPs to increase their understanding of the value of ultrasonography for scrotal abnormalities in combination with the biomarkers LDH, AFP and B-HCG in the differential diagnosis. Performing these diagnostics in time will increase the number of correct referrals for TC, and increase the chance that the 'two-week wait rule' will be met. Both actions, education of adolescent and young adult men and of GP's to increase knowledge and awareness of testicular cancer, and continuous medical education of GPs with respect to scrotal pathology may decrease patient' and doctor' delay, thus lower the percentage of TC patients diagnosed with advanced disease, decrease costs associated with treatment of advanced disease, and improve disease free and overall survival.

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Assessment of Volumetric Versus Manual Measurement in Disseminated Testicular Cancer; no Difference in Assessment Between Non-radiologists and Genitourinary Radiologist

Abstract

Background

The aim of this study was to assess the feasibility and reproducibility of semi-automatic volumetric measurement of retroperitoneal lymph node metastases in testicular cancer (TC) patients treated with chemotherapy versus the standardized manual measurements based on RECIST criteria.

Methods

21 TC patients with retroperitoneal lymph node metastases of testicular cancer were studied with a CT scan of chest and abdomen before and after cisplatin based combination chemotherapy. Three readers, a surgical resident, a radiological technician and a radiologist, assessed tumor response independently using computerized volumetric analysis with Vitrea software® and manual measurement according to RECIST criteria (version 1.1). Intra- and inter-rater variability were evaluated with intra class correlations and Bland-Altman analysis.

Results

Assessment of intra-observer and inter-observer variance proved non-significant in both measurement modalities. In particularly all intraclass correlation (ICC) values for the volumetric analysis were >.99 per observer and between observers. There was minimal bias in agreement for manual as well as volumetric analysis.

Conclusion

In this study volumetric measurement using Vitrea software® appears to be a reliable, reproducible method to measure initial tumor volume of retroperitoneal lymph nodes metastases of testicular cancer after chemotherapy. Both measurement methods can be performed by experienced non-radiologists as well.

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Introduction

Diagnostic process for testicular cancer (TC) includes physical examination, laboratory tests for tumor markers alpha-fetoprotein (AFP), betachoriongonadotropin (B-HCG), lactate dehydrogenase (LDH), and imaging tests, such as testicular ultrasound and computed tomography (CT) of abdomen and chest to assess regional and distant metastases. CT scans and tumor marker analysis make it possible to stage the extensiveness of disease and to classify the patient according to the International Germ Cell Consensus Classification (IGCCC)[1,2]. Staging results are fundamental in determining the prognosis and the optimal treatment strategy for each individual patient. Stage I nonseminomatous testicular germ cell tumor (NSTGCT) can be treated successfully with a wait-and-see policy, or unilateral nerve-sparing retroperitoneal lymph node dissection (RPLND), or one course of adjuvant cisplatin based combination chemotherapy after orchiectomy[2]. Disseminated disease is treated also with three or four courses of cisplatin based combination chemotherapy. Resection of residual retroperitoneal tumor masses (RRRTM) after chemotherapy is an essential part of the combined therapy of NSTGCT[3,4]. CT of chest and abdomen serve as the main diagnostic tool to determine pre- and post-chemotherapy tumor deposit size, allowing evaluation of the response to treatment and guiding the decision to perform RRRTM, either conventional or via laparoscopic surgery[5]. An alternative approach to surgery can be observing patients after systemic chemotherapy, certainly if abdominal residual tumor masses have become undetectable (lesions <1 cm) on CT scans and in some institution if the primary tumor did not contain teratoma components[6,7]. Residual metastatic disease after completion of chemotherapy can contain tumor necrosis, teratoma or viable germ cell cancer.

Optimal disease management is based on reliable and reproducible lesion measurement. Tumor response assessment has been standardized since the introduction of the bi-dimensional response criteria of the World Health Organization (WHO) which was more recently followed by one-dimensional (2D) response criteria based on RECIST (version 1.1), which is a set of rules defining overall tumor burden at baseline and objective tumor response and disease progression after systemic treatment[8,9].

In short, 2D measurements are obtained to assess the size of a tumor lesion. Measurements are obtained in the axial plane on a single slice, after careful selection from all axial planes in which the tumor lesion is visible. Assuming such single slice manual measurements in the axial plane comprise complete change in tumor size, neglects the fact that a tumor is an irregular three-dimensional lesion which

is not a perfect sphere and therefore can be a misinterpretation of tumor burden. Additionally, in literature high inter-observer and intra-observer variability in manual tumor assessment are reported because of the difficulty to define the outer borders of the lesion to be measured and the variation in perception of the largest diameter[10,11].

An approach to improve reproducibility of lesion size measurements, and to reduce time and effort of measurements, combined with rapid technological developments, have led to the development of software allowing semi-automated lesion segmentation of tumor masses[12,13]. Semi-automatic segmentation tools are utilized to acquire 3 dimensional (3D) images and accurate determination of tumor size alterations. Opposed to manual 2D measurements, in this 3D setting, asymmetrical tumor size changes can be detected and measured. Lymph node metastases are irregularly shaped and often closely located to adjacent tissue with similar contrast density. These characteristics, in combination with anatomical location and slice thickness, influence segmentation quality and increase measurement error, especially when measuring smaller shaped lesions[14,15]. The spread of TC to lymph nodes usually follows a predictable pattern with metastases occurring in retroperitoneal lymph nodes. Lymph node metastases in this region can be quite difficult to measure even with adequate contrast administrations and regular manual measurements, because of surrounding tissues with similar contrast densities causing indistinct borders of the tumor deposits[16]. Volumetric analysis is a new promising technique to measure a therapeutic response especially for lung and liver lesions, which can also be used to measure response of retroperitoneal lymph nodes of testicular cancer after chemotherapy[17].

The purpose of this pilot study was to assess the suitability and reproducibility of semi-automated volumetric analysis when applied to retroperitoneal lymph nodes in patients with disseminated TC, compared to 2D measurements based on RECIST between non-radiologists and a genitourinary radiologist.

Materials and Methods

We consulted the institutional review board of the UMCG, and they confirmed that no formal written waiver for the need of ethics approval was required because of the retrospective design of the study. Also there was no written consent needed from the patients. One of the supervising authors has had contact with some of the study participants as the surgeon who performed the resection of the lymph node metastases and therefore was a treating physician during a short period. This author did not perform the manual and volumetric measurements. Authors did not collect any personally-identifying information from study participants. Furthermore, all data were detached from patient information prior to analysis.

Study Population

CT scans of chest and abdomen of 21 consecutive nonseminomatous testicular cancer patients (NSTGCT), treated at the University Medical Center Groningen (UMCG), with a mean age of 36 (range 27-68) years undergoing resection of residual retroperitoneal tumor mass (RRRTM) after cisplatin based combination chemotherapy were evaluated. Of the 21 patients, 16 patients (76%) had stage II disease, 2 patients (10%) had stage III disease and 3 patients (14%) had stage IV disease. According to the International Germ Cell Consensus Classification (IGCCC) the majority of patients, 15 (71%) had disease with good prognosis, 4 patients (19%) intermediate prognosis and 2 (10%) poor prognosis.

Lesions outside the retroperitoneal area were not considered for this analysis. All patients had pre-and post-chemotherapy CT imaging performed at the UMCG or the referring hospital.

Finally 21 patients were eligible with 28 individual lesions identified in the retroperitoneum.

Data Collection

All post-chemotherapy CT scans were performed at the UMCG with a multi-slice CT scanner (Sensation S64, Siemens Healthcare, Forchheim, Germany) according to the TC protocol, which encompasses fasting 4-6 hours prior to the scan after which scanning of abdomen and thorax is performed with oral and intravenous contrast (100cc/flow 2.5). The reconstructed slice thickness for the standard protocol was 2.0 mm[18,19].

The majority of the pre-chemotherapy CT scans were performed in the referring hospitals. Depending on CT scanner quality and primary indication to perform a CT scan, reconstructed slice thickness was 2 mm for all scans.

All data were transferred to a dedicated advanced visualization workstation and were analyzed with a software package of Toshiba systems (Vitrea®/Vital Images, version 4)[20].

Vitrea® software is Vital Images' visualization software and commercially available for implementation. With this software 2D, 3D and 4D images are created of human anatomy from CT, MRI (magnetic resonance imaging) and PET (positron emission tomography) image data. The software provides options for cardiac, colon, vessel probe and other applications.

Evaluation of Retroperitoneal Lymph Node Metastases

All manual and semi-automatic measurements of the labeled retroperitoneal lymph node metastases were executed independently by 2 non-radiologists (surgical resident and radiological technician) blinded for patient data and each other's readings. These measurements were performed on a separate workstation without access to patient records. After transfer of CT scans to this separate workstation (without attachment of patient records), the readers measured the defined lesions while evaluating the CT images and performed the measurements. Tumor size was assessed based on RECIST criteria (1.1)[8,9].

The axial plane of the images chosen individually by each reader was used to draw long axis (LAD) and short axis (SAD) diameters in millimeters (Figure 1).

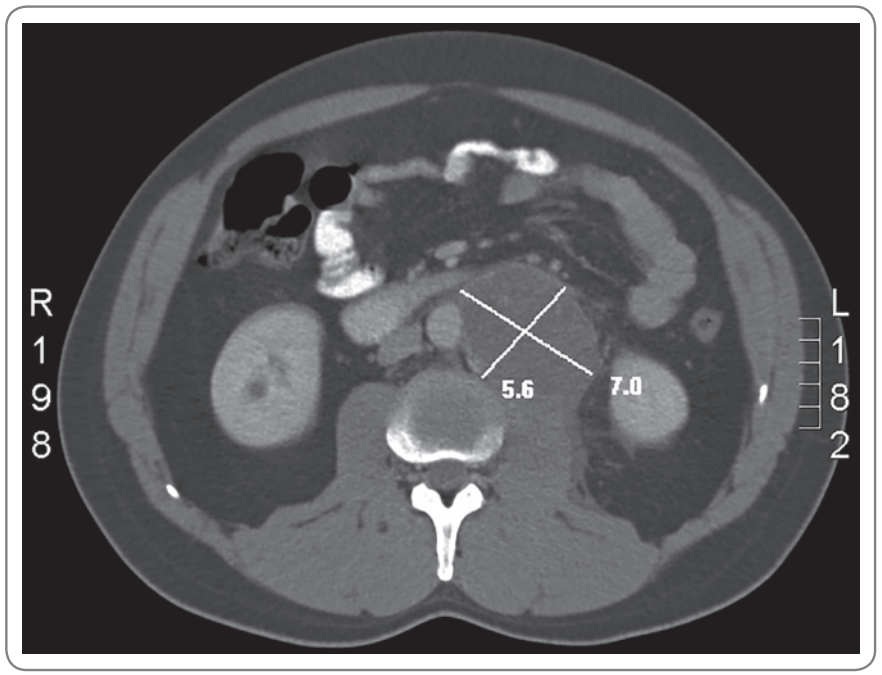

Figure 1.
Measurement according to RECIST in one dimension. Long axis and short axis measurement in mm is shown in the figure.

Semi-automatic evaluation of the retroperitoneal lymph nodes was also performed independently by the readers with Vitrea software®. This software package provided tools to perform volumetric measurements by semi-automatic segmentation on retroperitoneal lesions by manually selecting lesions in the axial and coronal plane followed by linear interpolation to create a 3D view. A nodule segmentation algorithm, based on radiodensity and grey scale differentiation, using Hounsfield unit values, is applied to separate the target lesions from background tissues and also morphological procedures are applied to separate these target lesions from adjacent tissue of the retroperitoneum. A visual assessment then followed on multi-planner reconstructions determining the contour of the lesion and in case of unsatisfactory segmentation manual adjustments could be made with correction tools if the lesion was not fully included in the segmentation field or if there was too much overlap of adjacent tissue (Figure 2). After satisfactory segmentation results, the software automatically generated and displayed a volume in cubic centimeters (cc).

Finally, an experienced genitourinary radiologist also performed manual 2D and semiautomatic 3D measurements to make comparisons versus measurements made by the non-radiologists.

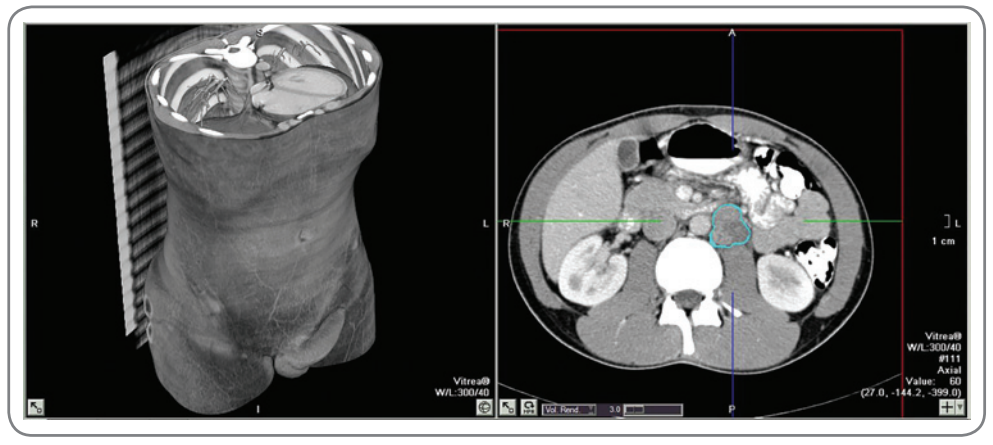

Figure 2.
Vitrea® semi-automatic volumetric analysis.

Statistical Analysis

Statistical analysis was performed with SPSS software version 18, City, US, Microsoft Excel, City, US. Measurement meant either the tumor diameter in mm or volume in cc. In order to attain geometrically equivalent entities, the sphere volume formula $V = \pi D^3/6$ was used to convert all volume measurements from mm^3 to effective (spherical) diameters in mm.

Table 1.
Patient characteristics and lesion distribution

Patient characteristics	
Patients (n)	21
Age median (range)	31 (22–63)
Lesions (n)	28
Stage II (%)	16 (76%)
Stage III (%)	2 (10%)
Stage IV (%)	3 (14%)
IGCCC good (%)	15 (71%)
IGCCC intermediate (%)	4 (19%)
IGCCC poor (%)	2 (10%)
Anatomical site	
RPAO (n)	1
CLRV (n)	14
LPAO (n)	10
CAV (n)	1
AOB (n)	2

Mean changes and range were calculated with SPSS. Descriptive statistics were used to summarize lesion characteristics and parameters (LAD, SAD, volume).
Intraclass correlation (ICC) values were used to assess intra-observer variation in the measurements according to RECIST and the volumetric method. Correlations were calculated to examine associations between the two measurement methods. Correlations with a coefficient <0.30 were considered weak, between 0.30-0.50 moderately strong, and >0.50, strong[21].
Intraclass correlation values were also applied to assess inter-rater variability of the two measuring methods. Furthermore, Bland-Altman analysis was performed to determine and visualize the inter-rater agreement between 2 readers. Bias (average difference between 2 readers), 95% confidence intervals and 95% limits of agreement were calculated.

Results

Radiologic Characteristics of the Retroperitoneal Lymph Nodes

Evaluation of CT scans of 21 patients, all diagnosed with NSTGCT, led to the identification of 28 individual retroperitoneal lymph nodes, which were analyzed manually and semi-automatically. Mean number of lymph nodes per patient was 1.5 (range 1-3). Distribution of lymph node size is presented in Table 1 and Figure 3. All these patients were in biochemical complete remission with normal tumor marker levels at time of the restaging CT-scan. Retroperitoneal lymph nodes which were resected either through a laparoscopic procedure or through a conventional laparotomy were localized as follows: 10 (35%) left paraaortic, 1 (4%) right paraaortic, 2 (7%) aortic bifurcation, 14 (50%) caudal of the left renal vein and 1 (4%) vena cava.
Table 2 provides an overview of the distribution of manual and volumetric measurement results as measured by 3 readers.

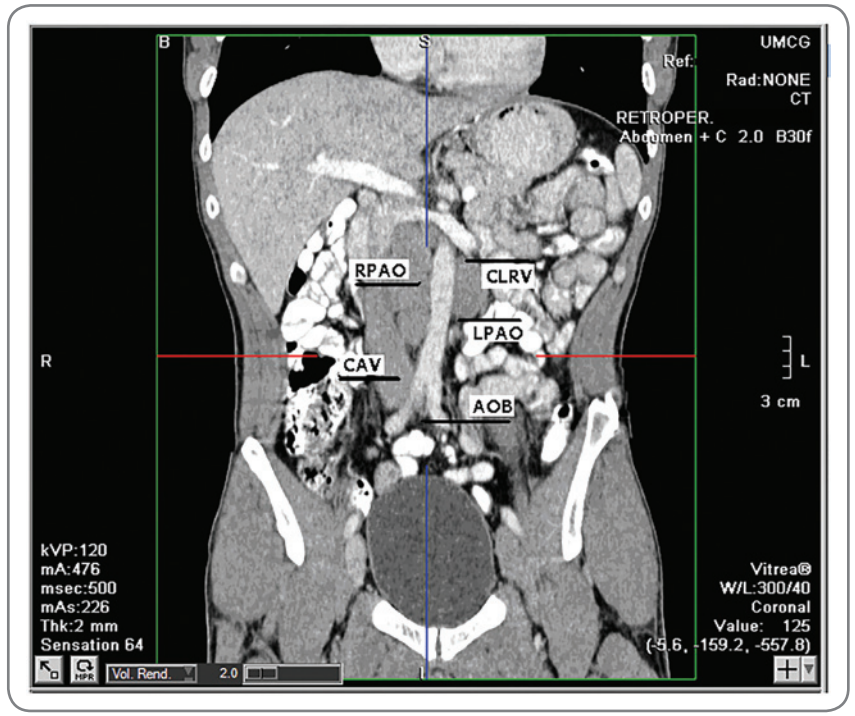

Figure 3.
Distribution of retroperitoneal lymph nodes.
**RPAO: right paraaortic, LPAO: left paraaortic, CLRV: caudal left renal vein, CAV: caval vein/vena cava, AOB: aortic bifurcation.*

Intra-observerVariability: Reproducibility by the Same Reader

Retroperitoneal lymph nodes were measured three times by 2 non-radiologist readers on the defined lesions. The ICC correlation for both readers was very significant with a correlation coefficient of .99 for reader 1 versus .98 for reader 2 with a corresponding P-value of <.001 for both readers.

Table 2.
Distribution of manual and volumetric lymph node measurements (mm)

Parameters	Observer 1	Observer 2	Radiologist
Pre chemo			
• LAD Mean ± SD	27.6±14.2	28.1±17.5	27.2±13.5
• LAD Median (range)	26.5 (8.2–76.4)	24.8 (7–91.3)	26.5 (5–70)
• SAD Mean ± SD	24.3±14.8	23.5±13.5	23±12
• SAD Median (range)	21.8 (4–75.9)	20.7 (6–67)	21.5 (5–56)
• Volume Mean ± SD	26.2±13.1	25.7±12.7	24.7±12.9
• Volume Median (range)	24.1 (8–70)	23.5 (8–68)	22 (7.8–69.8)
Post chemo			
• LAD Mean ± SD	21.9±14.4	21.3±13.7	21.1±14.3
• LAD Median (range)	17.9 (7.5–64.1)	16.7 (7–60)	17 (6–60)
• SAD Mean ± SD	18.9±13.5	17.9±13.6	17.8±13.7
• SAD Median (range)	14.6 (4.5–56.3)	13.5 (5.3–59)	13.5 (5–60)
• Volume Mean ± SD	20.7±11.9	20.5±11.6	19.2±11.7
• Volume Median (range)	17.3 (6.9–51.7)	16.9 (7.1–51.4)	15.5 (6.7–50.4)

Volumetric analysis was repeated three times for each individual lymph node by the two readers showing an almost 100% concordance for the individual measurements in axial and coronal plane. All ICC values were >.99 with a p-value of <.001.

Inter-observer Variability: Consensus between Readers

Absolute Measurements: Manual Measurement and Volumetric Method Compared

Mean of the absolute measurements was used to calculate ICC values between two readers (Table 3). ICC values show an excellent correlation for both measurement methods between these readers with a p-value of <0.001. Bland-Altman analysis (Figure 4) for testing the degree of agreement for manual as well as volumetric analysis shows minimal bias.

Measurements of both methods of the two readers were compared with measurements performed by an experienced radiologist. In Table 3 high ICC values are displayed. Results of the Bland Altman analysis are shown in Figure 4a-f. In this

Table 3.
Overview intra class correlation values between observers across methods

	ICC	P-value
Volumetric		
• Observer 1–2	.99	.000
• Observer 1-radiologist	.99	.000
• Observer 2- radiologist	.99	.000
Manual		
• Observer 1–2	.97	.000
• Observer 1-radiologist	.96	.000
• Observer 2-radiologist	.98	.000

graphical representation, degree of agreement is displayed with 95% limits between observers on both manual and volumetric measurements. From these plots it was concluded that the spread between points are between the limits of agreement for both methods.

Required Time to Perform Volumetric Analysis

Time needed to perform volumetric measurements was calculated for 2 readers. Median measurement time for reader 1 was 1.42 (0.37-3.66) minutes and for reader 2 was 2.69 (range 1.19-4.54) minutes. Time of lymph node selection and transfer to another workstation where Vitrea® analysis could be performed was approximately 10-15 minutes. Time to perform RECIST was not measured. Characteristics of the measurements of the radiologist are lacking.

Discussion

Measuring tumor burden and tumor response to therapy as accurate as possible in oncological practice remains a challenge. Limitations of manual measurements according to RECIST have been described in literature. An important limitation is that tumor measurement occurs at differently chosen slides by the readers, leading to a large intra- and inter-observer variation[10,11]. Volumetric images have gained importance in medical applications in recent years, resulting in software products allowing volumetric analysis. In liver surgery, volumetry is important to calculate postoperative liver volume and liver function resulting in safety enhancement of liver resection procedures[12,22,23].

In the present study radiological tumor response after chemotherapy in patients with disseminated nonseminomatous TC with retroperitoneal lymph node metastases was evaluated using two measurement procedures, namely 2D measurements based on the RECIST criteria and semi-automatic volumetric analysis with specialized computer software.

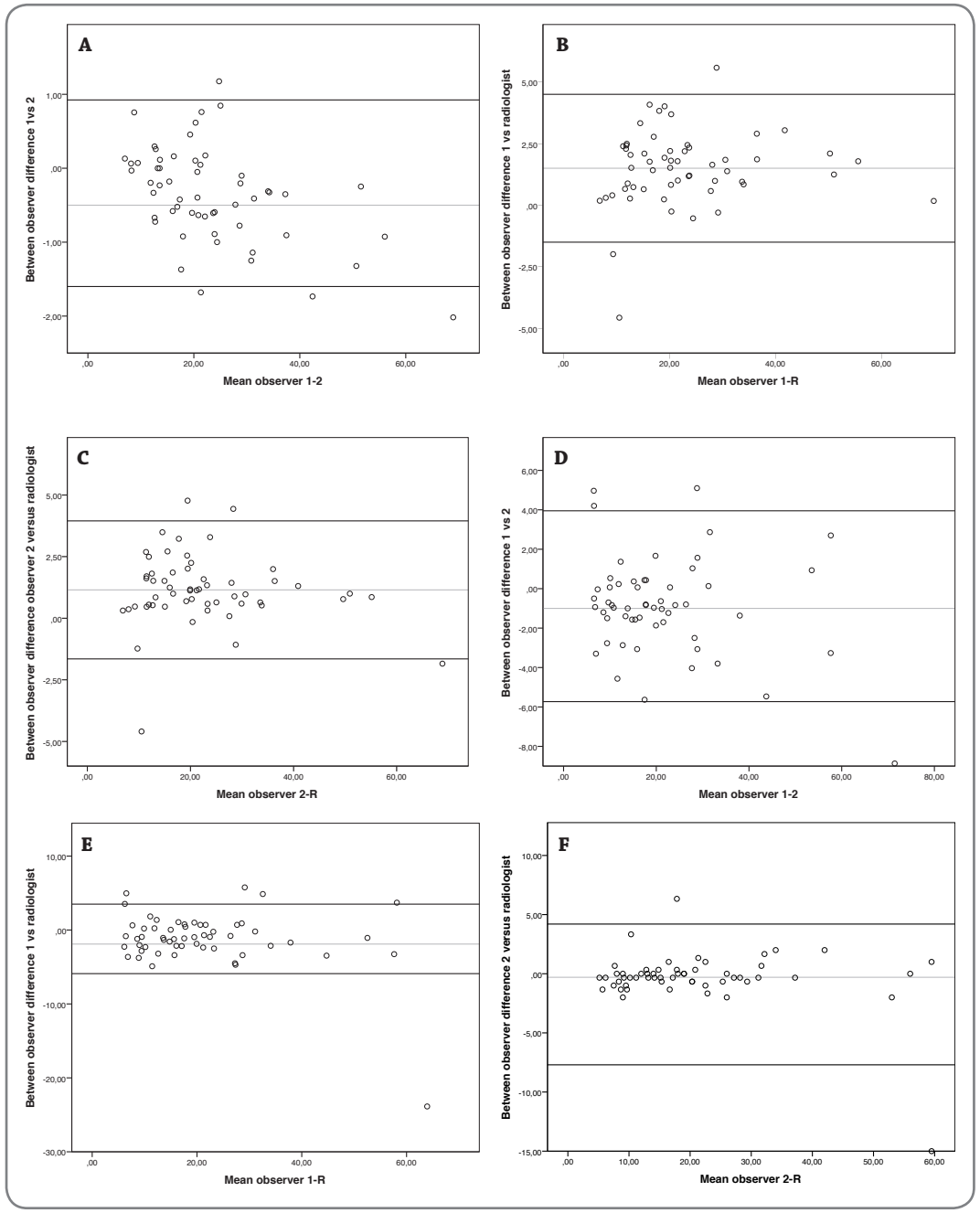

Figure 4.

Bland Altman plots. (a) Display Bland Altman plot observer 1 and 2 volumetric method (cc). (b) Display Bland Altman plot observer 1 and R (radiologist) volumetric method (cc). (c) Display Bland Altman plot observer 2 and R volumetric method (cc). (d) Display Bland Altman plot observer 1 and 2 manual method (mm). (e) Display Bland Altman plot observer 1 and R manual method (mm). (f) Display Bland Altman plot observer 2 and R manual method (mm). Mean difference and limits of agreement are displayed as reference lines.

Results show a high intra-observer agreement for the measured tumor volumes with the used software package. Measurement of the retroperitoneal lymph node volumes performed by each reader, both non-radiologists, showed also high correlations. This corresponds with findings of semi-automatic volumetric analysis in lung nodules which are promising and show reproducible measurements with high accuracy[24-26]. In the present study, intra-observer agreement for the 2D manual measurements was also high with ICC values of .99. In a previous study concerning intra-observer variability in the response evaluation according to RECIST in solid tumors such as breast cancer and colorectal cancer, correlation values ranged between 0.76-0.96[27]. Intra-observer agreement with these manual measurements in the current study was higher than expected based on previous literature on this subject.

In the present study, user experience was assessed by measuring inter-observer agreement. Measurements were performed by non-radiologists as well as a radiologist to evaluate its user friendliness and reliable application in the routine hospital. Inter-observer variability for semi-automatic measurements was comparable for manual measurements, with acceptable limits of agreement. When we looked at absolute measurement values both measurement modalities were highly reliable. In another study, inter-observer variability was significantly lower in the semi-automatic method[28].

Good results were obtained with volumetric analysis with a high level of agreement between observers and methods. It should be taken into account that the complexity of the parameters still require a lot of work to produce an informative and reliable image. Also, volumetric analysis of lymph node metastases compared to, for example, lung nodules can be more difficult since lymph node metastases are often irregularly shaped with inhomogeneous contrast enhancement and are in the proximity of similar density tissues.

Tumor volumetry can be time consuming because of the segmentation process. However in experienced hands of, a radiologist, a radiological technician or a resident the time investment seems appropriate. Also, results from this study showed that novices with some radiological experience and an experienced assessor such as a radiologist were both able to reliably predict tumor volume using the semi-automatic computer software. This validation study has been conducted in a center of expertise for patients with testicular cancer for over more than three decades. In present times there is a paradigm shift in the radiologic evaluation of lesions. Where in the past the executing surgeon relied 100% on the readings of a radiologist, nowadays the surgeon and a surgical team need tools to get a quick and reliable impression of lesions before performing a specific surgery. We have found that the volumetric method can be performed by an experienced non-radiologist as

well and that the required time to obtain and measure a reliable 3D image is under 3 minutes. Such a study for volumetric measurements is lacking in literature for retroperitoneal lymph node metastases in testicular cancer. The new technology facilitates the surgical-oncologist or the uro-oncologist in the conventional or laparoscopic surgical treatment planning of the resection of tumor masses.

In conclusion, the pilot study showed that radiological technicians and (surgical/urology) residents could perform volumetric and manual measurements in a reliable manner with a high intra and inter-observer reliability. With the increase in the number of cancer patients receiving chemotherapy, automatic and semiautomatic segmentation tools will likely play an important role in the evaluation of tumor response to treatment, e.g. a cost-effective way to measure tumor response and prepare the surgical or uro-oncologist in the resection of retroperitoneal lymph node metastases. For now, clinical guidelines based on manual measurement in 2D in the axial plane according to RECIST criteria remain the standard method for assessing a radiological tumor response to anti-cancer therapy. This study has shown that the volumetric method is reproducible, user friendly and is promising as a more accurate method in the surgical field since it provides a 3D view. Especially the latter can make a clinical difference with more detailed surgical planning and can contribute to achieving better outcomes in patient care. Since tumor response criteria for volumetric measurements are not yet validated, combining the clinical outcome in a larger prospective study group could provide standardized volumetric measurements.

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Laparoscopic Resection of Residual Retroperitoneal Tumor Mass of Nonseminomatous Testicular Germ Cell Tumors

Abstract

Background

Resection of a residual retroperitoneal tumor mass (RRRTM) is standard procedure after combination chemotherapy for metastatic nonseminomatous testicular germ cell tumors (NSTGCT).

Methods

At the University Medical Center Groningen, 79 consecutive patients with disseminated NSTGCT were treated with cisplatin based combination chemotherapy between 2005 and 2007. Laparoscopic RRRTM was performed for patients with RRTM located less than 5 cm ventrally or laterally from the aorta or the vena cava. The 29 patients who fulfilled the criteria had a median age of 25 years (range, 16–59 years). The stages of disease before chemotherapy treatment according to the Royal Marsden classification were 2A (n = 6, 21%), 2B (n = 14, 48%), 2C (n = 3, 10%), and 4 with a lymph node status of N2 (n = 6, 21%).

Results

The median duration of laparoscopy was 198 min (range, 122–325 min). The median diameter of the RRTM was 21 mm (range, 11–47 mm). Laparoscopic resection was successful for 25 patients (86%). Conversion was necessary for three patients (10%): two due to bleeding and one because of obesity. One non-planned hand-assisted procedure (3%) also had to be performed. Histologic examination of the specimens showed fibrosis or necrosis in 12 patients (41%), mature teratoma in 16 patients (55%), and viable germ cell cancer in 1 patient (3%). The median hospital stay was 1 day (range, 1–6 days). During a median follow-up period of 47 months (29–70 months), one patient experienced an early relapse (1 month after the end of treatment) (4%).

Conclusion

For properly selected patients, laparoscopic resection of RRTM is an improvement in the combined treatment of disseminated NSTGCT and associated with a short hospital stay, minimal morbidity, rapid recovery, and a neat cosmetic result. Long-term data to prove oncologic efficacy are awaited.

Çiğdem Öztürk, Robert J. van Ginkel, Ruby M. Krol, Jourik A. Gietema, Hendrik S. Hofker, Harald J. Hoekstra
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Introduction

Treatment for nonseminomatous testicular germ cell tumors (NSTGCT) has developed enormously over the past 30 years, leading to an improved prognosis with an overall 10-year survival rate of almost 90%[1]. Disseminated disease is treated with cisplatin based combination chemotherapy that comprises three or four courses of bleomycin, etoposide and platinum (BEP), according to the International Germ Cell Consensus Classification (IGCCC) prognosis group[2,3].

Surgical resection is the gold standard for managing postchemotherapy residual retroperitoneal tumor masses in advanced NSTGCT. The aim of surgery is to resect the residual retroperitoneal tumor mass (RRTM) and other residual disease localizations such as lung metastases[4,5]. The policy with regard to the extent of surgery for residual masses after chemotherapy is subject of ongoing discussion with a surgical spectrum that ranges from excision of only visible abnormal masses[6,7] to a full bilateral retroperitoneal lymph node dissection (RPLND)[8,9]. Proponents of a full bilateral RPLND state that patients with advanced NSTGCT are at high risk for tumor in lymph nodes not included in modified RPLND because areas of teratoma or carcinoma are difficult to visualize intraoperatively. However, literature confirms that modified postchemotherapy RPLND for well-defined residual masses is a safe surgical and oncologic procedure with less morbidity[7,10].

After chemotherapy, mature teratoma and viable residual tumor are the main arguments for surgery. An alternative approach to surgery can be observation of patients with NSTGCT after systemic chemotherapy. Models for predicting post-chemotherapy residual mass histology have been proposed to determine the patients for whom surgery should be considered[11,12]. Noninvasive attempts have been made to predict "reliably" the viability of residual tumor tissue after chemotherapy using magnetic resonance imaging (MRI) and, more recently, positron emission tomography (PET)[13]. Nevertheless, because reliable predictions about necrosis, fibrosis, mature teratoma, or viable germ cell cancer in the residual metastases cannot be made, adjuvant surgery with resection of residual disease still is indicated. Traditionally, open full-template non nerve-sparing RPLND was the standard practice. This approach was associated with complications related to invasive surgery, particularly damage to the sympathetic ganglia, hypogastric nerves, or postganglionic nerve fibers. These complications were responsible for sexual morbidity, mainly anejaculation and erectile disturbances[14]. Currently, the morbidity is low, and preservation of sexual and ejaculatory function is highly reliable with either a template- or nerve-sparing complete RPLND, especially in high-volume centers[15]. The median postoperative hospital stay is 6 days[16].

Higher morbidity with open RPLND and the general benefits of laparoscopy such as decreased blood loss, less pain, better cosmetic results, and a shorter postoperative hospital stay have led to the introduction of laparoscopic RPLND. On a modest scale, laparoscopic RPLND is performed primarily for the staging and possible treatment of testicular cancer, mainly in stage 1 disease[17-19]. With further refinement of laparoscopic techniques, several centers also have described the benefits of the laparoscopic procedure for stage 2 disease after completion of chemotherapy[20-26].

At the University Medical Center Groningen (UMCG), the feasibility of resecting RRTM laparoscopically was explored and evaluated as a minimally invasive surgical technique applied in the field of adjuvant surgery in the combined treatment of testicular cancer.

Materials and Methods

From October 2004 to August 2007, 79 consecutive patients with disseminated NSTGCT were treated using cisplatin based combination chemotherapy at the UMCG. Before chemotherapy, the patients were staged according to the Royal Marsden classification system based on spiral computed tomographic (CT) findings of the abdomen as well as on chest and tumor marker analysis. Patients received three or four courses of BEP depending on their IGCCC classification[2,3].

After completion of chemotherapy, when the patients had achieved complete biochemical remission (90%), they were restaged with a spiral CT of the abdomen and chest. Of the 79 patients, 53 (67%) showed a complete biochemical response with residual disease. Afterward, 45 patients (57%) had surgery, primarily resection of a residual retroperitoneal tumor mass (RRRTM) (51%).

Table 1 summarizes the baseline characteristics and outcome data for all 79 consecutive patients. Eight patients with residual disease and a complete response (10%) did not undergo surgery because of extended disease in multiple organs (n = 6), mediastinal disease (n = 1), or irresectable massive retroperitoneal residual disease (n = 1).

Patient selection for laparoscopic RRRTM was based on the size and location of the residual tumor. Patients with a residual retroperitoneal tumor mass with a diameter smaller than 50 mm shown on CT and located ventrally or laterally from the aorta or vena cava were candidates for laparoscopic resection of these abnormalities. Retroperitoneal tumor masses posterior to the great vessels were not candidates for laparoscopic resection.

Table 1.

Patient baseline characteristics and outcome data for all 79 consecutive nonseminomatous testicular germ cell cancer patients with disseminated disease treated with cisplatin based combination chemotherapy at the University Medical Center Groningen between October 2004 and August 2007

Age; median (range) in years	29 (18-63)	
Stage of disease according to Royal Marsden; n (%)	Stage II	43 (54%)
	Stage III	4 (5%)
	Stage IV	31 (39%)
	Unknown	1 (1%)
Prognosis (IGCCC); n (%)	Good	46 (58%)
	Intermediate	22 (28%)
	Poor	10 (13%)
	Unknown	1 (1%)
Tumor response after chemotherapy; n (%)		
Complete biochemical response:		71 (90%)
• without residual disease		18 (23%)
• with residual disease		53 (67%)
◦ no surgery of residual disease		8 (10%)
◦ surgery of residual disease		45 (57%)
▪ retroperitoneal		40 (51%)
▪ lungs		5 (6%)
No normalization of tumor markers		5 (6%)
Biochemical relapse within one month		1 (1%)
No completion of chemotherapy		2 (3%)
Outcome/survival status; n (%)		
◦ No evidence of disease		68 (86%)
◦ Alive with disease		4 (5%)
◦ Died of disease		6 (8%)
◦ Died of other causes		1 (1%)
Follow up after chemotherapy; median (range) in months		
◦ For all 79 patients		52 (3-75)
◦ For 72 patients (excluding 7 patients who died)		53 (21-77)

On the basis of these selection criteria, 29 patients with a median age of 25 years (range, 16–59 years) underwent an adjunctive laparoscopic RRRTM. The characteristics of these patients are summarized in Table 2. The primary tumor location was in the left testicle of 16 patients (55%) and in the right testicle of 13 patients (45%). The median follow-up period in this study was 47 months (range, 29–70 months). During the same period, 11 patients underwent conventional laparotomy for RRRTM (Figure 1). Eight patients had residual retroperitoneal disease too large for laparoscopic resection, and for three patients, a laparoscopic procedure was not opportune because of the tumor location.

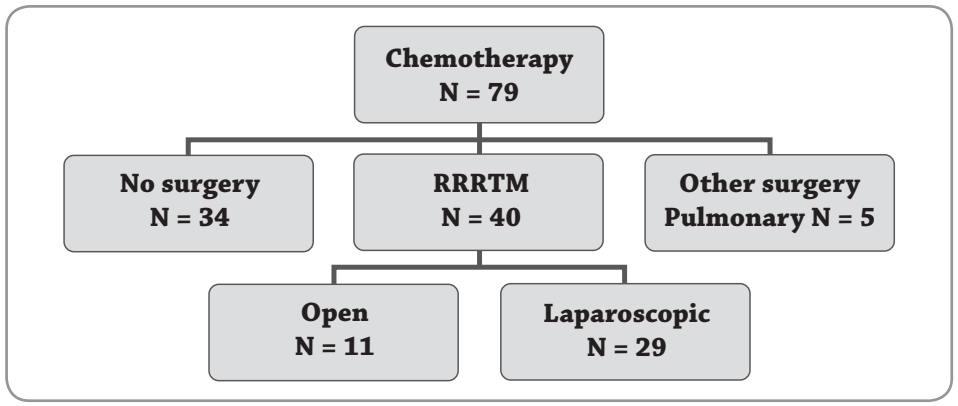

Figure 1.

Flowchart of patients with disseminated testicular cancer receiving cisplatin based combination chemotherapy (October 2004–August 2007).

Laparoscopic Procedure

Preoperatively, no intestinal preparation was done, and no prophylactic antibiotics were administered. Laparoscopic resection was performed by experienced laparoscopic surgical oncologists. The patients were placed supine with both legs abducted in the "French" position (also called the lithotomy position) or in a half right lateral position depending on the site of the RRTM. In the case of a predominant pericaval residual tumor mass, the patients underwent surgery in the French position. Periaortic and-left sided masses were resected with patients in the half-right lateral position. Patients with bilateral RRTM were again placed in the French position. Pneumoperitoneum was created using an open technique, and the first 10-mm blunt tip trocar was situated paraumbilically (for the camera). Additionally, a 5-mm trocar was placed in the suprapubic region and a 10-mm trocar in the left lower

abdomen. Another 5-mm trocar was inserted into the epigastrium (Figure 2).

Dissection was performed using the Harmonic ultrasonic cutting device (Ethicon-Endosurgery, Cincinnati, OH, USA). During the laparoscopic approach, the colon was mobilized to expose the aorta, the vena cava, or both. The anatomic landmarks were the renal vein, the ureter, and the iliac vessels. Care was taken to avoid the lumbar vessels in the retroaortic region, with the aim to prevent autonomic nerve damage.

After exposure of the retroperitoneum and identification of the RRTM, extension of the surgical resection consisted of excising the RRTM only without unilateral dissection according to templates. An EndoCatch (Covidien, Manfield, MA, USA) was used to remove the surgical specimen.

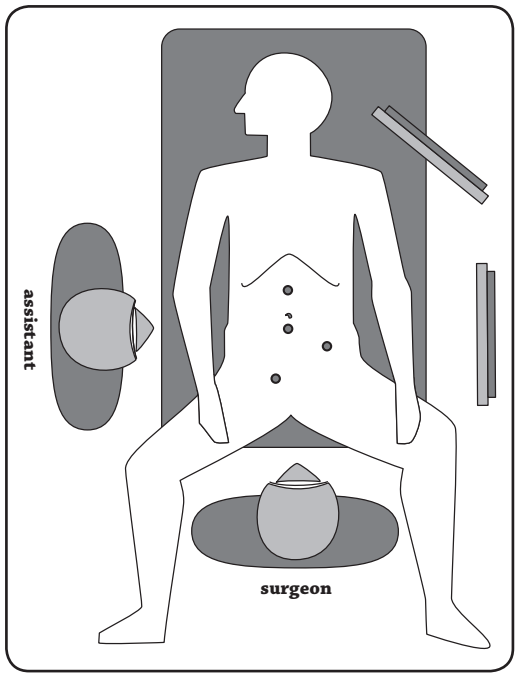

Figure 2.

Operative technique. Positioning of patient ("French" position) and team.

Intraoperative frozen section analysis of the specimen was not performed. No drains were used. The aim was to perform non-hand-assisted procedures. Conversion was performed when complications arose or when the surgical oncologist had the impression that the RRTM could not be removed completely using laparoscopy. After laparoscopic resection, the patients were followed in the same manner as patients after conventional resection. A strict follow-up protocol according to European Society for Medical Oncology guidelines was carried out by the medical oncologist. This protocol included a monthly clinical assessment and tumor marker determination during the first postoperative year, followed by a gradually tapering schedule (every 2 months the second year, every 3 months the third year, every 6 months the fourth year, then annually thereafter). A CT scan of the chest and abdomen was performed in case of clinical or biochemical signs of a recurrence or for patients who were marker negative at the initial presentation of disseminated disease. Operative time, complications, transfusion rate, conversion to open surgery, and duration of hospital stay were analyzed.

Table 2.

Individual characteristics of 29 nonseminomatous testicular cancer patients treated with laparoscopic resection of residual retroperitoneal tumor mass (RRRTM)

Pat (No)	Age (yrs)	Side primary tumor	Histology primary tumor	Stage Royal Marsden	IGCCC	Diameter Retroperitoneal mass pre-CT (mm)	Chemo-therapy	Diameter RP mass post-CT (mm)	RRRTM	OR time (min)	Compli-cation	PO-stay hospital (days)	Histology RRTM	FU (mo)	Outcome
1	27	Left	1,3	IIB	1	20	4 (B)EP	12	L	195		3	N/F	70	NEDd
2	18	Left	3	IIB	1	41	4 (B)EP	16	L	198		1	N/F	66	NED
3	35	Left	1,4	IIC	1	70	3 BEP	41	C a	280		1	T	59	NED
4	25	Left	1,3	IIB	1	32	3 BEP	26	L	188		1	T	49	NED
5	23	Left	1,4	IV	1	20	4 BEP	15	L	186		1	N/F	49	NED
6	22	Right	1,3	IIB	2	50	3 BEP	17	L	215		1	T	54	NED
7	25	Right	1,3	IIA	1	12	3 BEP	30	L	280	Chylous leakage	1[c]	T	48	NED
8	25	Left	1,2,3	IV	1	38	3 BEP	23	L	198		2	T	52	NED
9	17	Left	1,2,3	IIB	1	33	4 BEP	17	L	248		1	T	50	NED
10	18	Left	1,3,4	IV	3	53	4 (B)EP	46	L	187		1	N/F	51	NED
11	23	Left	1,3	IIB	1	34	3 BEP	11	L	148		1	N/F	47	NED
12	20	Right	1,3	IIA	1	17	3 BEP	30	C	276	Bleeding iliac artery	4	T	47	NED
13	28	Right	2,3,4	IIB	1	33	4 (B)EP	13	L	168		2	T	48	NED
14	30	Right	5	IIC	2	62	4 BEP	41	L	325		1	T	51	NED
15	41	Right	1,3	IIA	1	10	3 BEP	22	L	200		1	N/F	48	NED
16	31	Left	1,2	IIB	1	26	3 BEP	17	L	246		1	T	47	NED

Table 2. Continued

Pat (No)	Age (yrs)	Side primary tumor	Histology primary tumor	Stage Royal Marsden	IGCCC	Diameter Retroperitoneal mass pre-CT (mm)	Chemo-therapy	Diameter RP mass post-CT (mm)	RRRTM	OR time (min)	Compli-cation	PO-stay hospital (days)	Histology RRTM	FU (mo)	Outcome
17	27	Left	1,3	IIB	1	47	3 BEP	30	L	160		1	N/F	38	NED
18	30	Left	1,2,3	IIB	1	32	3 BEP	12	L	220		1	N/F	41	NED
19	59	Left	1,2,3,4	IV	1	38	4 BEP	47	L	184		1	T	42	NED
20	16	Right	1,3	IIC	2	78	4 (B)EP	36	L	190	Anejacu-lation	1	T	43	NED
21	34	Right	3,4	IV	1	31	3 BEP	12	L	229		1	N/F	41	Relapse/ NED[e]
22	41	Right	1,2,3,4	IIA	1	17	3 BEP	33	C	149	Bleeding aorta	6	VT	41	NED
23	26	Right	1	IIA	1	14	3 BEP	13	L	222		2	N/F	41	NED
24	30	Left	1,2	IIB	2	34	4 BEP	17	L	210	Bleeding testicular vene	1	N/F	36	NED
25	29	Left	1,2,3	IIA	1	19	3 BEP	11	L	122		1	T	41	NED
26	22	Right	1,2	IIB	1	27	3 BEP	21	L	133		1	T	34	NED
27	26	Right	1,2,3,4	IIB	1	29	3 BEP	33	L	202		1	T	37	NED
28	20	Left	1,2,3	IIB	2	32	3 BEP	23	L	152		1	T	29	NED
29	42	Right	6	IIB	1	121	3 BEP	40	C b	282		5	N/F	36	NED

Histology primary tumor: 1:embryonal carcinoma, 2:yolk sac tumor, 3:teratoma ,4:seminoma, 5: burnout germ cell tumor, 6: leydig hyperplasia. Histology RRTM: N/F: necrosis/fibrosis, T: teratoma, VT: viable germ cell cancer. [a] *Converted to hand-assisted procedure,* [b] *Converted to a laparotomy due to impossibility of creating a good exposure in an obese patient,* [c] *Readmission after 3 weeks for 13 days and after 4 months for 16 days,* [d] *No evidence of disease,* [e] *Relapse one month after laparoscopy, 6 months after completion of chemotherapy, 41 months NED.*

Results

All 29 patients included in the laparoscopic treatment group had a biochemical complete remission after chemotherapy. Cisplatin based combination chemotherapy elicited a reduction of the retroperitoneal metastases with a mean factor of 0.6, resulting in a median postchemotherapy tumor size of 21 mm (range, 11–47 mm) (Table 2). In almost two thirds of the patients, the residual tumor was located in the latero-aortic region. The median interval between the last chemotherapy course and the laparoscopic resection of RRTM was 3 months (range, 1–6 months). For 25 patients (86%), the laparoscopic procedure could be conducted as planned. For 3 patients (10%), conversion to open surgery was necessary due to a slight bleeding from the common iliac artery, a larger bleeding from the aorta, and the impossibility of creating a good exposure in an obese patient. In another patient (3%), the initial plan was changed because extreme obesity prevented the creation of a window sufficiently large for laparoscopic exploration, and a hand-assisted laparoscopic resection of the tumor was performed. The only minor perioperative complication encountered was an injury of the testicular vein at the left side, which was managed laparoscopically with clips.

The median duration of surgery for the 29 patients, including positioning of the patient, was 198 min (range, 122–325 min). When the three patients who had conversion to laparotomy and the one patient who underwent a hand-assisted procedure were excluded, the median duration of a successful laparoscopic resection was 195 min (range, 122–325 min). The estimated blood loss was minimal (<50 ml), except for the converted patient with bleeding from the common iliac artery who did not need blood transfusion and the converted patient with bleeding from the aorta who lost up to 1,500 ml of blood. The median postoperative hospital stay was only 1 day (range, 1–6 days). The longest postoperative hospital stay (6 days) was experienced by the patient who had to undergo conversion due to injury of the aorta. During preparation of the two residual tumor masses from the aorta, a large bleeding occurred. Laparoscopy was quickly converted to a laparotomy, and the diathermic injury to the aorta was managed with two sutures. This procedure required a total operative time of 149 min. No postoperative infections occurred. One short-term postoperative complication (3%) included a massive chylous ascites which could not be treated conservatively. After 4 months, laparoscopic exploration showed visible leakage of a lymph vessel, which was coagulated successfully with argon diathermia and clipped. One patient had anejaculation after laparoscopic RRRTM. Histologic examination showed necrosis or fibrosis in 12 patients (41%) and teratoma in 16 patients (55%). In one patient (3%), a radically resected viable germ cell cancer was found. Preoperatively, this patient received three courses of BEP, and after complete laparoscopic RRRTM, no additional chemotherapy courses were given. During the median follow-up period of 47 months (mean, 46 months; range, 29–70 months), one short-term local recurrence was experienced by a 34-year-old man in the good risk prognosis group who had mature, immature teratoma and seminoma elements in his right-sided primary tumor. This man received three courses of BEP. Cisplatin based combination chemotherapy resulted in a biochemical complete remission and was followed by a laparoscopic RRRTM. Residual tumor masses were located on the left side next to the aorta and between the aorta and the vena cava. Histology showed fibrosis. The man's tumor markers were slightly elevated 1 month after laparoscopy and 6 months after completion of chemotherapy. A CT scan showed recurrence between the aorta and the vena cava (Figure 3). Additional chemotherapy (paclitaxel, ifosfamide, and cisplatin) was administered, and the patient achieved a complete response, both biochemically and radiologically. A laparotomy with a formal template dissection on both sides was performed. Histology of the specimen showed fibrosis. No signs of recurrence were detected 41 months after the man's last surgery.

Discussion

Laparoscopic RPLND was first described in 1992 for a patient with stage I NSTGCT[17]. With further development of laparoscopic techniques and experience performing them, laparoscopic RPLND was introduced in several specialized centers for the staging and treatment of mainly low-stage testicular cancer, with the same boundaries of dissection as an open approach. Table 3 summarizes the results reported by these centers[20-26]. The results show

Figure 3.
Abdominal computed tomography (CT) scan of retroperitoneal recurrence.

Table 3.
Comparison of postchemotherapy studies

Series	Year	N	Stage	Conversion (N)	Complication Peri-operative (N)	Complication post-operative (N)	Operative time (min)	Hospital stay (days)	Retroperitoneal recurrence (N)	Distant relapse (N)
Rassweiler[20]	1996	8	2 IIB 6 IIC	6 (75%)	?	1 (13%)	357	7	none	none
Palese[21]	2002	7	2 IIA-B 3 IIB 1 II C 1 III	2 (29%)	4 (57%)	none	411	2	none	none
Steiner[22]	2004	68	10 IIA 43 IIB 15 IIC	0 (0%)	0 (0%)	28 (17%[a]	243	3,7	1 (1%)	none
Albqami[23]	2005	59	43 IIB 16 IIC	0 (0%)	9 (15%)	11 (19%)	234	3,8	1 (2%)	none
Permpongkosol[24]	2007	16	3 IIA 8 IIB 2 IIC 2 IIIA 1 IIIB	2 (13%)	4 (25%)	3 (19%)	318	2	none	1 (6%)
Maldonado-Valadez[25]	2007	16	2 IIA 6 IIB 2 IIC 6 III	0	0	0	237	4.7	1	none
Calestroupat[26]	2009	26	16 IIA-B 13 IIC	3 (12%) [b]	9 (35%) [c]	none	183	5	none	none
Current series	2007	29	6 IIA 14 IIB 3 IIC 6 IV	4 (14%)[b]	3 (10%)[c]	2 (7%)	198	1	1 (4%)	none

[a] *Complications in a total of 185 patients, stage 2 included.*
[b] *Including one conversion to a hand-assisted procedure.*
[c] *One minor injury of the testicular vein and 2 bleedings leading to conversion.*

that the laparoscopic approach is feasible, with minimal morbidity, rapid recovery, and a neat cosmetic result. However, long-term oncologic results and equivalence of the laparoscopic RRRTM to the conventional procedure are not fully established. At the UMCG, laparoscopic RPLND has been performed since 2005 for well-selected cases. Two thirds of the patients with RRTM appear to be candidates for laparoscopic resection of RRTM.

The current study aimed to investigate our results regarding laparoscopic resection of RRTM, which was performed successfully for 11 to 47 mm masses in 25 of the 29 selected patients. The postoperative complication rate was 7% due to postchemotherapy chylous ascites after RPLND, a not unusual complication with an incidence of 2%[27] and anejuculation experienced by one patient. The median hospital stay was one day. In addition, neat cosmetic results were achieved.

During the same study period, 11 patients treated at the UMCG with cisplatin based combination chemotherapy for disseminated NSTGCT did not fulfill the laparoscopic inclusion criteria and were scheduled for conventional surgery consisting of laparotomy with resection of the retroperitoneal tumor mass. The median postoperative stay for these 11 patients who underwent a laparotomy for RRTM was 6 days (range, 2–9 days), which is comparable with the median hospital stay after laparotomy reported in the 1980s[16].

As mentioned earlier, four procedures (14%) could not be performed (completely) according to plan. The conversion rate for seven reported series varied from 0-75% and was 14 % (4 patients) in the current series (Table 3)[20-26]. These four conversions included a non-planned hand-assisted laparoscopic procedure and a laparotomy because of technical difficulties based on obesity of the patients. Two other conversions to a conventional laparotomy were required due to bleedings, which included one slight bleeding of the iliac artery and a larger bleeding originating from the aorta. Residual retroperitoneal tumor masses are sometimes extensively attached to surrounding tissues, making a good resection extremely difficult to achieve. This can explain the occurrence of bleedings, such as the bleeding from the aorta. This risk of a bleeding possibly is higher with laparoscopic procedures than with open procedures, so adequate patient selection with evaluation of the tumor characteristics is important. In most cases, laparoscopic techniques are sufficient for handling bleedings, and conversion is not needed. In the current study, one bleeding originating from the testicular vein could be managed laparoscopically. The patient was discharged from the hospital 1 day postoperatively. In another study, 9 of 59 patients (43 stage 2B, 16 stage 2C) experienced a bleeding during laparoscopy not requiring a conversion[23]. In the series of Steiner et al.[22], 68 patients underwent laparoscopy after two or three courses of chemotherapy without the need for any conversion. However, these authors did convert 2.4% of the stage I patients. These patients had not received preoperative chemotherapy. In a small series of Rassweiler et al.[20], six (75%) of eight patients with stage 2C disease who underwent postchemotherapy laparoscopy, a conversion to a laparotomy was performed because of desmoplastic reaction around the aorta and the vena cava as

a result of chemotherapy[28,29]. Permpongkosol et al.[24] had to convert procedures due to vascular injury in 2 (12.5%) of 16 patients who had received three or four courses of chemotherapy (Table 3).

The median duration of the laparoscopic procedure in the current series was 198 minutes, compared with 216-348 minutes described in literature. Furthermore, the median postoperative hospital stay was 1 day compared with median hospital stay ranging from 2 to 8.2 days in other laparoscopic series. These other series also included patients who had conversion to a laparotomy, thus explaining the discrepancy with our results.

Currently, very few institutions have reported laparoscopic RRRTM after chemotherapy for disseminated NSTGCT. Our first experience with this new technique was favorable. The minimal morbidity, the short postoperative hospital stay, and the neat cosmetic results are a step forward in the combined treatment of testicular cancer. Although we have achieved good results over the past 30 years with conventional RRRTM, it appears that this also is possible with laparoscopic resection for patients with minimal RRTM. Approximately 70% of disseminated testicular cancer patients who require RRRTM are candidates for complete laparoscopic resection based on the current selection criteria. However, it is unknown whether the laparoscopic procedure will result in more frequent (short or late) relapses. In the current series, one patient (4%) had a short-term relapse. The recurrence was located between the vena cava and the aorta. Preoperative CT scan images showed an RRTM located on the left side of the aorta between the aorta and vena cava. Although this RRTM was resected during laparoscopy, residual tissue remained behind, causing outgrowth of viable germ cell cancer. This relapse can be calculated as a technical failure. Short- and long-term relapses after chemotherapy are mostly related to incomplete resection of residual disease and also are encountered after conventional surgery[30]. The limitation of this study is that the oncologic efficacy of the procedure remains questioned because the long-term oncologic follow-up data are not equivalent to those for the open procedure. In the future, after more patients have been treated with laparoscopic resection, data will become available with reliable relapse figures. This potential pitfall requires prolonged and very stringent follow-up assessment to monitor the oncologic safety of the laparoscopic resection of RRTM. It is important to perform thorough follow-up assessment to be certain that a minimally invasive intervention does not involve the risk of so-called extratemplate disease[31].

An overshadowing component of our study is the controversy surrounding the surgical management of patients with NSTGCT and concerns about the development of late relapsing abdominal teratoma[29]. Late-recurring disease is characterized by slow growth, production of alphafetoprotein, chemoresistance, and a poor prognosis[28]. Our surgical management of patients with NSTGCT conforms to the European guidelines for testicular cancer[27].

Although our results and those of others are favorable, questions remain: Is laparoscopic RRRTM as complete oncologically as an open procedure? How long should we wait before laparoscopic RRRTM is proclaimed as the standard, or should a randomized study be performed? Particularly the rapid postoperative recovery, the low morbidity, and the neat cosmetic results contribute to the well-being of the usually young patients, most of whom still have many years ahead of them. Whatever policy is chosen for the treatment of patients with advanced NSTGCT, management should take place at a referral center with specific expertise in the treatment of testicular cancer and an oncologic team of specialists.

Conclusion

Laparoscopic RRRTM after chemotherapy for disseminated testicular cancer is a feasible surgical treatment option with a short hospital stay and neat cosmetic results for well-selected patients. Which patients are the right candidates for laparoscopic RRRTM remains the question. Close and long-term follow-up assessment of long-term results with respect to tumor recurrence is obligatory.

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Laparoscopic Resection of Residual Retroperitoneal Tumor Mass in Advanced Nonseminomatous Testicular Germ Cell Tumors; a Feasible and Safe Oncological Procedure

Abstract

Background

To describe the 10 year experience and oncological results of the University Medical Center Groningen with conventional laparotomy (C-RRRTM) and laparoscopy (L-RRRTM) to resect residual retroperitoneal tumor masses (RRTM) in a large series of patients with advanced nonseminomatous testicular germ cell tumors (NSTGCT).

Methods

From 2005-2015, 150 consecutive patients with disseminated NSTGCT required adjunctive surgery after completion of chemotherapy. Patients with RRTM <5 cm ventral/lateral from the aorta and/or the caval vein were candidates for L-RRRTM. Remaining patients received C-RRRTM.

Results

L-RRRTM was scheduled in 89 patients (median age 27 [range 16-66] years) and C-RRRTM in 61 patients (median age 28 [range 16-64] years). Median residual tumor diameter was 20 (range 5-70) mm in the L-RRRTM versus 42 (range 11-220) mm in the C-RRRTM group (p <.001). Conversion in the L-RRRTM group was performed in 14 patients (15%). Perioperative complications occurred in 5 patients (6%) in the L-RRRTM and 7 (12%, NS) in the C-RRRTM group. Median duration of L-RRRTM was 146 (range 45-288) minutes vs. 221 (range 95-792) minutes for C-RRRTM (p <.001). 9/75 patients (12%) in the L-RRRTM group had postoperative complications versus 26/75 patients in the C-RRRTM group (including conversions) (35%, p <.001). Median postoperative stay in the L-RRRTM group was 1 (range 1-5) vs. 5 (3-26) days in the C-RRRTM group (p <.001). During a median follow-up of 79 (2-144) months, 27 patients had recurrences:4 (5%) in the L-RRRTM group and 23 (31%) in the C-RRRTM group (p <.001).

Conclusions

Laparoscopic resection of RRTM after cisplatin based combination chemotherapy for advanced NSTGCT is feasible and oncologically safe in selected patients, with shorter hospital stays and good oncological and excellent cosmetic outcomes.

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Introduction

The introduction of cisplatin based combination chemotherapy to treat advanced nonseminomatous germ cell tumor (NSTGCT) has impacted survival rates greatly, with an overall 10-year survival rate of up to 90%[1,2]. Surgery plays a pivotal role in the treatment of residual retroperitoneal tumor masses (RRTM) as well as pulmonary residual disease in NSTGCT and is aimed at resecting viable germ cell cancer tissue and/or teratoma[3-7]. The extent of surgery has remained controversial for many years, with a surgical spectrum varying from a full bilateral retroperitoneal lymph node dissection (RPLND) to a more limited approach with resection of visible abnormal retroperitoneal tumor masses[8,9]. Today's literature supports that a modified post chemotherapy RPLND, e.g. resection of well-defined residual retroperitoneal tumor masses (RRRTM), is a safe oncological procedure, with less morbidity and it conserves sexual functioning in the majority of these patients[10-12].

Classically, RPLND or RRRTM was executed through a midline laparotomy. Laparoscopic RPLND (L-RPLND) was first performed in 1992. In the past decade, it has emerged as an alternative to reduce morbidity associated with conventional open surgery using the same boundaries of dissection. Laparoscopic surgery is mainly described in literature for stage I disease as a diagnostic procedure and for the resection of low volume disease[13-16]. In an earlier pilot study, the Groningen study group showed that the laparoscopic approach was feasible, with a low rate of retroperitoneal relapse in advanced testicular cancer in properly selected patients[17]. So far, there are no large consecutive series of disseminated testicular cancer patients described with respect to the results of adjunctive surgery; e.g., conventional versus laparoscopic resection of RRTM. For the laparoscopic resection of RRTM to be considered a safe alternative oncologic procedure compared to conventional open surgery in patients with advanced NSTGCT, long-term follow up assessments in a larger cohort are required.

The current study aimed to describe the 10-year experience of the Comprehensive Cancer Center of the University Medical Center Groningen UMCG with conventional resection of RRTM (C-RRRTM) and laparoscopic resection of RRTM (L-RRRTM) in a consecutive series of patients, with a focus on operative outcomes and oncologic results, and to define oncological and technical boundaries for laparoscopic management in the field of adjunctive surgery after cisplatin based combination chemotherapy in patients with testicular cancer.

Methods

A total of 296 disseminated patients with NSTGCT were treated at the Department of Urology, Surgical Oncology and Medical Oncology, of the UMCG between 2005 and 2015. Of these 296 patients, 150 underwent resection of RRTM after 3 or 4 cycles of cisplatin based combination chemotherapy. All patients were prospectively studied. Until 2004, the UMCG gold standard was RRRTM using a conventional midline laparotomy. The results of this policy with respect to the oncological, sexual, and psychosocial outcomes were previously described[4,5,12]. Laparoscopic resection of RRTM was introduced at the UMCG in 2004. The selection criteria for L-RRRTM were based on tumor size and the localization of the residual mass and were described previously in the pilot report[17]. In short, patients were candidates for a laparoscopic approach if the RRTM was less than 5 cm in diameter and located ventrally or laterally from the aorta, caval vein, or iliac vessels. Incidentally, a slightly larger RRTM up to max 7 cm at a favorable paraaortic anatomical location was accepted for laparoscopic resection. In these cases, a higher risk for conversion was considered and discussed with the patient before the procedure. Patients with a RRTM posterior to the great vessels and/or a tumor mass larger than 5 cm were not considered candidates for laparoscopy. A flow diagram of the current series of 296 patients with NSTGCT scheduled for L-RRRTM or C-RRRTM is presented in Figure 1. Also presented in Figure 1 are the number of converted procedures from laparoscopy to open (LC-RRRTM group).

Surgical Procedure

The surgical procedure, excising only visible abnormal retroperitoneal tumor masses, has been extensively described previously in the feasibility report[17]. Key points regarding the laparoscopic procedure are that patients were positioned in the "French" or in a half-right lateral position depending on the localization of the RRTM[4,5,17]. Surgical resection comprised only the resection of the RRTM and conversion was performed in case of technical difficulties due to patient and/or tumor characteristics and/or complications.

Factors leading to conversion were classified into two categories; reactive conversion (RC), which is defined as one that follows an intraoperative event such as bleeding, and pre-emptive conversion (PC), which is defined as a conversion undertaken to avoid complications such as unclear anatomy, obesity, and a time-consuming laparoscopy procedure without any 'surgical progress' during the resection of the RRTM.

Conventional resection was performed with the same oncological principles, excising only visible abnormal retroperitoneal tumor masses[3-7].

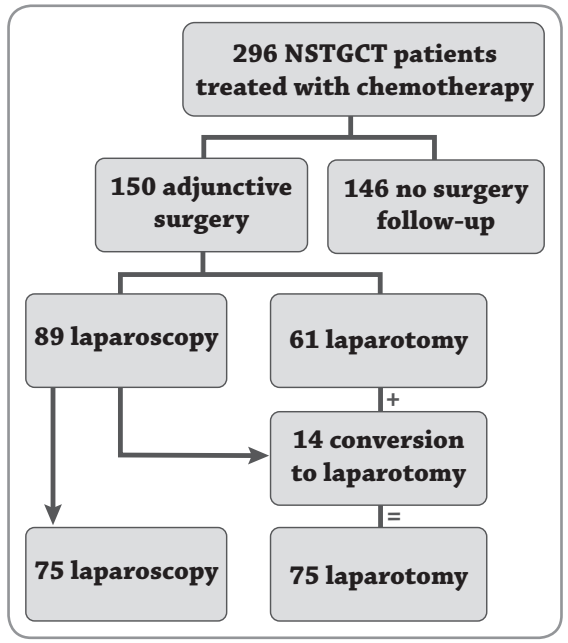

Figure 1.
Patient flow chart of all 296 consecutive NSTGCT patients with disseminated disease treated with 3 of 4 courses of cisplatin based combination chemotherapy at the UMCG between 2005 and 2015.

Postoperative procedure

Direct postoperative follow up was performed at the UMCG by the Department of Surgical Oncology and long-term follow up by the Department of Medical Oncology according to the guidelines of the European Society for Medical Oncology (ESMO). Within this protocol, a monthly clinical and tumor marker evaluation was performed over the first year, followed by a gradually tapering schedule, with annual evaluations from years 5 to 10. Computed tomography was done 6, 12, and 24 months after complete resections and 6, 12, 24, and 60 month after incomplete resections.

Statistical Analysis and Assessment of Complications

A prospective dataset, including the previously described patients[17], was constructed of all patients undergoing L-RRRTM or C-RRRTM from 2005 to 2015 comprising all patient and treatment-related information. Intra- and post-operative complications were categorized using administrative and electronic medical records. Patients were asked with regular intervals about symptoms of retrograde ejaculation during outpatient clinic visits and these events were recorded. Statistical differences between the two groups were analyzed using the chi-squared test for dependent variables and Mann–Whitney's U test or univariate analysis. Survival analysis was performed using the Kaplan-Meier method with the log rank test. All tests were double sided, and p values <0.05 were considered to indicate significance.

Results

Pre-operative Characteristics

The post-chemotherapy, pre-operative patient and tumor characteristics of the 150 patients (median age 27 [range 16-66] years) are presented in Table 1. The most common primary histology was embryonal carcinoma (n = 99, 66%). There were no statistically significant differences between the primary histology in the two groups except for embryonal carcinoma in the L-RRRTM group (p <.001). Patients with good prognoses according to the International Germ Cell Cancer Collaborative Group (IGCCCG), were more likely to undergo L-RRRTM than C-RRRTM (81% vs. 29%; p <.001). The majority of patients treated with L-RRRTM had clinical stage II disease (68 patients [77%] vs. 31 patients [51%] in the C-RRRTM group; p <.05). The most common residual tumor location was paraaortic (86, 57%); 69% in the L-RRRTM group versus 41% in the C-RRRTM group (p = .001). The median residual tumor size was significantly smaller in the L-RRRTM group; 20 (5-70) mm vs. 42 (11-220) mm in the C-RRRTM group (p <.001).

Operative and Outcome Characteristics

Eighty-nine patients with a median RRTM mass of 20 (range 5-70) mm and for whom the vast majority (n = 72, 81%) belonged to the IGCCCG good risk category, were scheduled for laparoscopic resection of the RRTM with the intention of resecting it. In 14 of 87 patients (15%), a conversion to open, conventional surgery was necessary. In 11 patients, pre-emptive conversions (12%) were performed due to technical difficulties (n = 7) and patient-related factors (n = 4). In 3 patients, reactive conversions (3%) were performed due to complications that occurred intraoperatively: ureter injury, aortic bleeding, and vena cava bleeding, respectively.

In more detailed analyses, the outcome was analyzed based on the L-RRRTM group (75 patients), the laparoscopic conversion LC- RRRTM group (14 patients), and the C-RRRTM group (61 patients) as presented in Table 2.
The median residual tumor size in the L-RRRTM group was 19 (5-57) mm versus 29 (16-70) mm in LC- RRRTM group, and 42 (11-220) mm in the C-RRRTM group (p <.01). Paraaortic RRTM location was found significantly more often in the group scheduled for L-RRRTM (61 vs. 25 in the C-RRTM group; p <.05).
No significant differences were found in perioperative complications between the 89 patients scheduled for L-RRRTM (5 patients [6%]; 1 ureter injury, 4 patients with >500 mL blood loss) and the 61 patients scheduled for C-RRRTM (7 patients [12%]; 1 ureter injury, 6 patients with >500 mL blood loss) (p <.19). Seventeen postoperative

Table 1.
Preoperative patients' and tumor characteristics

Variable	L-RRRTM N = 89	C-RRRTM N = 61	p value
Age (median, range) yrs	27 (16-66)	28 (16-64)	.11
Histology compounds testis tumor; n (%)			
Seminoma	28 (32)	13 (21)	.29
Immature teratoma	31 (35)	11 (18)	.07
Mature teratoma	46 (52)	28 (46)	.69
Embryonal carcinoma	73 (82)	26 (43)	<.001
Chorioncarcinoma	6 (7)	8 (13)	.11
Yolk sac	41 (46)	17 (28)	.05
IGCCCG risk score before chemotherapy; n (%)			
Good	72 (81)	18 (29)	<.001
Intermediate	12 (13)	26 (43)	
Poor	5 (6)	17 (28)	
Stage (Royal Marsden); n%			
IIA	15 (17)	1 (2)	<.05
IIB	41 (46)	11 (18)	
IIC	12 (14)	19 (31)	
III	2 (2)	13 (21)	
IV	19 (21)	17 (28)	
Residual tumor location; n (%)			
Paraaortic	61 (69)	25 (41)	.001
Paracaval	9 (10)	11 (18)	
Interaortocaval	16 (18)	21 (34)	
Iliac	3 (3)	4 (7)	
Diameter RRTM mm (median range)	20 (5-70)	42 (11-220)	<.001

L-RRRTM, laparoscopic resection residual retroperitoneal tumor mass.
C-RRRTM, conventional resection residual retroperitoneal tumor mass.
N/F, necrosis and/or fibrosis.

Table 2.
Operative Characteristics: 2005-2015 laparoscopic and conventional surgery

Variable	L-RRRTM N = 75	LC-RRRTM N = 14	C-RRRTM N = 61
Median RRTM diameter, mm (range)	19 (5-57)*	29 (16-70)	42 (11-220)*
Residual tumor localisation; n (%)			
• Paraaortic	51 (68)#	10 (72)	25 (41)#
• Paracaval	7 (9)	2 (14)	11 (18)
• Interaortocaval	14 (19)	2 (14)	21 (34)
• Iliac	3 (4)	0	4 (7)
Postoperative complications; n (%)	9 (12)#¶	8 (57)¶	18 (30)#
• None	66 (88)	6 (43)	43 (70)
• Wound infection	2	2	6
• Chylous leakage	1	2	5
• Pulmonary infection	0	1	0
• Urinary complications	4	0	1
• Haemorrhage/haematoma	1	0	0
• Thromboembolism	0	1	0
• Ileus	0	1	1
• Retrograde ejaculation	1	1	5
• Incisional hernia	0	0	0
Residual tumor histology; n (%)			
• N/F	25 (33)	8 (57)	26 (43)
• Teratoma +/- N/F	38 (51)	4 (29)	26 (43)
• viable germ cell cancer +/- teratoma	12 (16)	2 (14)	9 (14)
Operative time; minutes, median (range)	146 (45-288)¶#	217 (111-341)#	221 (95-792)¶
Hospital stay; days, median (range)	1 (1-5)¶[a]	5 (3-13)[a]	6 (3-26)¶

L-RRRTM, laparoscopic resection residual retroperitoneal tumor mass.
LC-RRRTM, laparoscopic converted resection residual retroperitoneal tumor mass.
C-RRRTM, conventional resection residual retroperitoneal tumor mass.
** p <.01, # p <.05, ¶, p <.001, [a] p <.001.*

complications (19%) occurred in those scheduled for L-RRRTM (n = 89), and 18 postoperative complications (30%) occurred in those scheduled for C-RRRTM (n = 61) (p = .14). Nine postoperative complications occurred in the L-RRRTM group (n = 75, 12%) versus 8 in the LC-RRRTM group (n = 14, 57%) (p <.001) and 18 in the C-RRRTM group (n = 61, 30%) (p <.05). Overall, there were 9 postoperative complications in the final L-RRRTM group (n = 75; 12%) and 26 postoperative complications in the final C-RRRTM group (n = 75; 35%, p <.001). Patients in the LC-RRRTM and C-RRRTM groups were more likely to develop wound infections, chylous leakage, pulmonary infections, and retrograde ejaculation.

The different histologies of the resected RRTM for L-RRRTM, LC-RRRTM, and C-RRRRTM groups are presented in Table 2. The median operative time in the L-RRRTM group was 146 (45-288) minutes versus 217 (111-341) minutes in the LC-RRRTM group (p <.001) and 221 (95-792) minutes in the C-RRRTM group (p <.001). The median length of hospital stay for the L-RRRTM group was 1 (1-5) day vs. 5 (3-13) days in the LC-RRRTM group (p <.001) and 6 (3-26) days in the C-RRRTM group (p <.05).
The histopathology of the resections for recurrent disease showed necrosis/fibrosis in 6 (22%) patients, viable germ cell cancer in 7 patients (26%), teratoma in 12 patients (44%), and yolk sack with glandular differentiation in 1 patient (4%). Five patients with viable germ cell cancer at the time of recurrence were in the C-RRRTM group versus one patient in the L-RRRTM group. Four of these 5 patients had also viable germ cell cancer in their initial RRRTM pathology results. A detailed overview of the 27 patients with recurrences is summarized in Table 3.

The median follow up for all 150 NSTGCT patients after RRRTM was 79 (range 2-144) months. Twenty-seven of 150 patients had recurrences (18%). Four patients (5%) in the L-RRRTM group (n = 75 excluding the conversions) and 23 patients (31%) in the C-RRRTM group (n = 75 including the conversions) (p <.001) had recurrences. The oncological outcome is presented in detail in Table 4. Of the 27 patients with recurrent disease, 26 (96%) received (combined) treatment; 16 (59%) had surgery alone, 9 had (33%) systemic chemotherapy plus surgery, 1 (4%) had only systemic chemotherapy, and 1 (4%) had no treatment.
The disease-free survival (DFS) and overall survival (OS) of all patients and those initially scheduled for L-RRRTM (n = 89) and C-RRRTM (n = 61) and those finally treated with L-RRRTM (n = 75) and C-RRRTM (including the 14 converted laparoscopy patients) are presented in Figures 2a, 2b, 2c, and Figures 3a, 3b, 3c. Significant differences were found in OS and DFS between the initially scheduled and final treatment groups.

Table 3.
Characteristics of 27 nonseminomatous testicular cancer patients with relapse

Pat (No)	Age (yrs)	Side primary tumor	Histology*	Stage Royal Marsden	IGCCCG	Diameter RRTM (mm)	Location RRTM	Histology §	FU since RRTM (mo)	Months until first relapse	Treatment relapse	Histology relapse surgery §	Outcome
L-RRRTM													
1	33#	Right	3,4	IV	1	11	interaortocaval	N/F	113	9	CTX, RRRTM	N/F	NED
2	30	Right	1,2	IV	1	17	interaortocaval	T,VT	98	11	RRRTM	T	NED
3	27	Left	1,3	II	1	46	paraaortic	T,N/F	97	61	CTX		AWD
4	29	Right	1,2	II	1	21	interaortocaval	VT	18	14	CTX, RRRTM	VT	NED
LC-RRRTM													
5	41#	Right	1,2,3,4	II	1	21	paraaortic	T,VT	113	46	RRRTM	T	NED
6	37	Left	1,4	IV	2	29	paraaortic	N/F	106	1	CTX, horacotomy	N/F	NED
7	20	Left	1,2	II	1	16	paracaval	N/F	96	9	RRRTM	N/F	NED
8	27	Left	1,3	II	1	29	paraaortic	N/F	51	36	RRRTM	T	NED
C-RRRTM													
9	27	Left	1	III	1	17	paraaortic	T	109	27	RRRTM	T	NED
10	37	Right	6	IV	3	15	paracaval	T	107	96	RRRTM	VT	AWD
11	19	Left	1,2,3	IV	2	160	paraaortic	T	116	2	Thoracotomy	T	NED
12	38	Right	3	III	2	15	paraaortic	N/F	34	6	Thoracotomy	N/F	NED
13	28	Right	3	IV	2	80	interaortocaval	T,N/F	105	5	CTX, resection mass neck	T	NED
14	26	Left	1,3	II	2	30	interaortocaval	T	96	13	RRRTM	T	NED

Table 3. Continued

Pat (No)	Age (yrs)	Side primary tumor	Histology*	Stage Royal Marsden	IGCCCG	Diameter RRTM (mm)	Location RRTM	Histology §	FU since RRTM (mo)	Months until first relapse	Treatment relapse	Histology relapse surgery §	Outcome
15	24	Left	1,2,3	III	3	31	paracaval	T/VT	26	9	Thoracotomy	VT[a]	DOD
16	53	Left	5	II	2	80	iliac	VT	7	1	No treatment options	-	DOD
17	33	Left	2,3	III	2	84	interaortocaval	T/VT	90	5	Thoracotomy	T	NED
18	22	Left	5	III	2	65	paraaortic	T/VT	89	52	CTX, RRRTM	VT,T	NED
19	21	Right	1,2,3	II	1	47	iliac	T	68	10	CTX, RRRTM	T	DOD
20	31	Left	1	III	1	69	interaortocaval	T	89	3	RRRTM	T	NED
21	28	Right	1,2	IV	3	16	paraaortic	N/F	67	7	CTX, RRRTM	N/F	NED
22	28	Left	3	II	1	35	paraaortic	T	19	7	CTX, RTX RRRTM	VT[a]	DOD
23	23	Left	3	II	3	220	paraaortic	T,VT	58	8	CTX, RRRTM	VT	NED
24	24	Right	3	III	3	220	interaortocaval	T,N/F	45	4	Thoracotomy	T	NED
25	20	Right	1,2	II	1	29	iliac	T	33	10	RRRTM	T	NED
26	37	Left	3,4	III	1	96	paraaortic	T,VT	25	8	Thoracotomy	N/F	NED
27	23	Left	1,2,3	IV	2	25	paraaortic	T,N/F	103	103	RRRTM	VT, T	NED

*L-RRRTM: laparoscopic resection residual retroperitoneal tumor mass, LC-RRRTM: laparoscopic converted resection residual retroperitoneal tumor mass, C-RRRTM: conventional resection residual retroperitoneal tumor mass. # previously reported[17] * Histology: 1: embryonal carcinoma, 2: yolk sac tumor, 3: teratoma, 4: seminoma, 5: burnout lesion, 6: unknown. § Histology: N/F: necrosis/fibrosis, T: teratoma, VT: viable germ cell cancer, [a] embryonal rhabdomyosarcoma (transformation from mature teratoma). CTX: chemotherapy, RTX: radiotherapy. NED: no evidence of disease, AWD: alive with disease; DOD dead of disease.*

Table 4.
Outcome characteristics: 2005-2015 laparoscopic and conventional surgery

Variable	L-RRRTM N = 75	LC-RRRTM N = 14	C-RRRTM N = 61
Follow up; months, median (range)	93 (7-144)#	71 (15-113)	70 (2-140)#
Recurrence; n (%)	4 (5)[a]	4 (29)	19 (31)[a]
Survival status; n (%)			NS
• No evidence of disease	73 (97)	14 (100)	54 (88)
• Alive with disease	1 (1.5)	0	1 (2)
• Died of disease	1 (1.5)	0	5 (8)
• Died of other causes	0	0	1 (2)

L-RRRTM, laparoscopic resection residual retroperitoneal tumor mass.
LC-RRRTM, laparoscopic converted resection residual retroperitoneal tumor mass.
C-RRRTM, conventional resection residual retroperitoneal tumor mass.
NS: non significant, # p <.05, [a] p <.001.

Discussion

This is currently the largest series published in literature with respect to laparoscopic resection of RRTM after cisplatin based combination chemotherapy for metastatic NSTGCTs. In cases of RRTM after chemotherapy for metastatic NSTGCT, adjunctive resection of all residual tumor mass is an essential part of the combined treatment to cure these patients[3-7]. In an earlier pilot study, the Groningen study group showed that the laparoscopic approach was feasible in properly selected patients with advanced NSTGCT, with surgical resection comprising of only the resection of the RRTM[17]. However, the study included a relatively small cohort of patients, and longer follow up data are lacking with respect to disease free survival. The current report includes the previously described patients[17].
Since the introduction of laparoscopic RPLND in 1992, and with the further development and increasingly routine use of laparoscopic techniques, the minimally invasive approach is gaining interest in the treatment of mainly lower-stage testicular cancer. The nine studies published to date are summarized in Table 5[14,18-25].

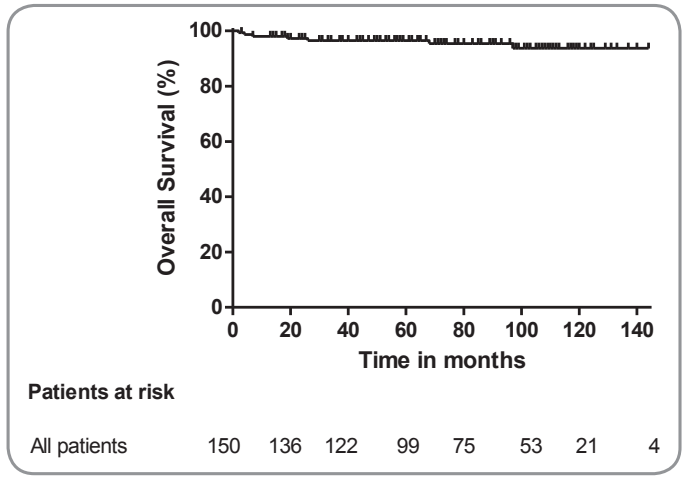

Figure 2a.
Overall Survival after RRRTM: all patients.

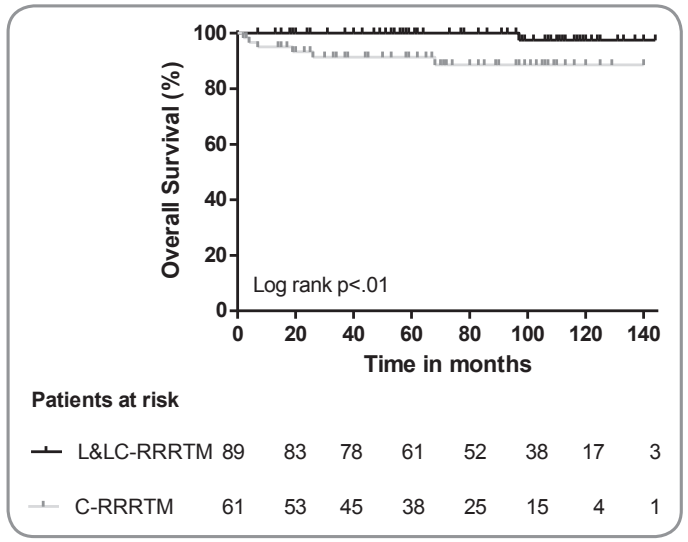

Figure 2b.
Overall Survival after initial L-RRRTM versus initial C-RRRTM: Log rank p <.01.

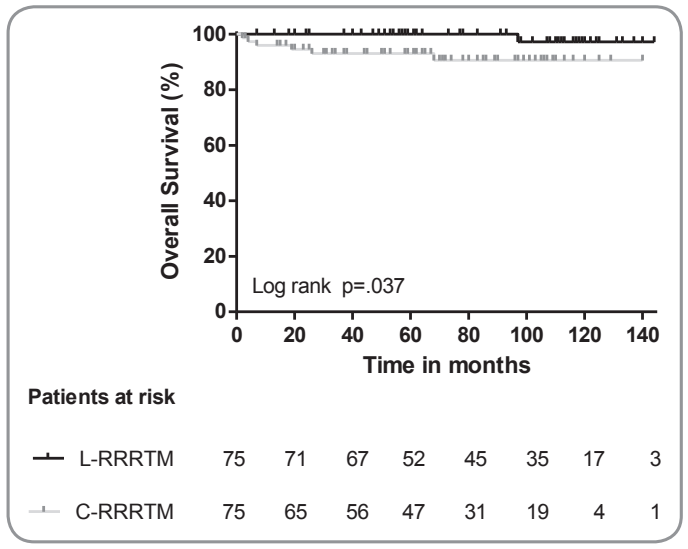

Figure 2c.
Overall Survival after final L-RRRTM versus final C-RRRTM: Log rank p <.05.

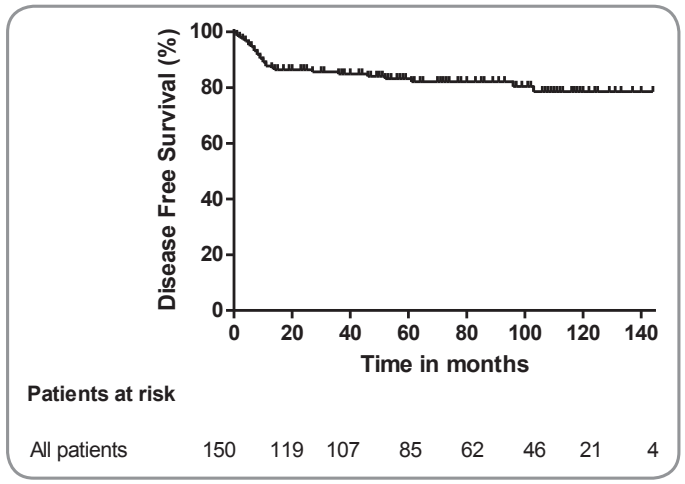

Figure 3a.
Disease Free Survival after RRRTM; all patients.

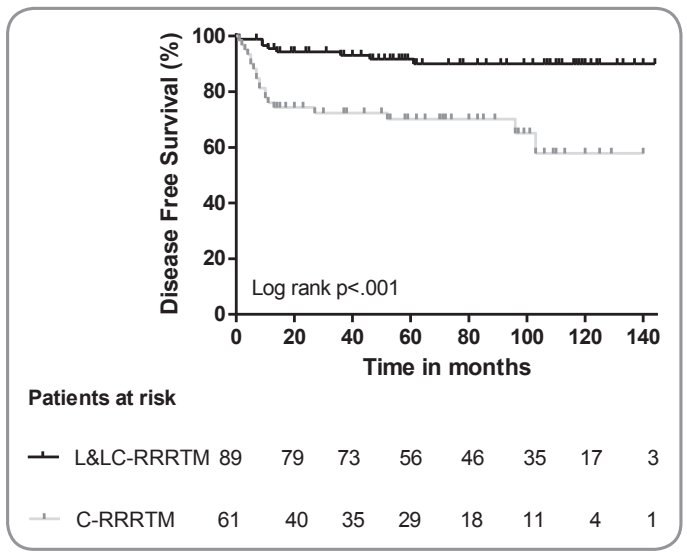

Figure 3b.
Disease Free Survival after initial L-RRRTM versus initial C-RRRTM: Log rank p <.001.

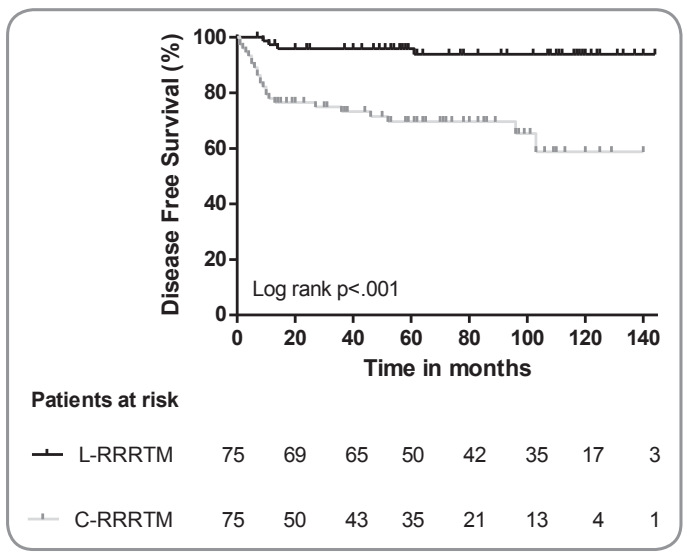

Figure 3c.
Disease Free Survival after RRRTM after final L-RRRTM versus final C-RRRTM: Log rank p <.001.

In the present study, analysis of the L-RRRTM group was done in parallel with that of the C-RRRTM group. The L-RRRTM group consisted of successfully performed laparoscopies (n = 75) and the C-RRRTM group (n = 75) included the LC-RRRTM patients. Statistical analysis performed between these groups should be evaluated in a more descriptive fashion since this was not a randomized trial and selection bias indisputably exists, leading to confounding factors such as the IGCCCG category and amount of residual disease after chemotherapy.
A significant difference in median RRTM diameter was found between the group scheduled for L-RRRTM (20 [range 5-70] mm) versus the group scheduled for C-RRRTM (42 [11-220] mm; p <.001). This significant difference is in line with the study by Busch et al where the RRTM diameter was 22 mm in the L-RRRTM group versus 68 mm in the C-RRRTM group[21].
Although the conversion rate in the literature varied in the past from 0% to up to 75%, the current UMCG conversion rate of 15% is in line with current conversion rates varying from 0% to 13%[14,18-25]. In general, the conversion rate decreases with surgical experience but increases with the size of the RRTM. The UMCG conversion rates in the current series are slightly higher than that of the previous pilot report (15% vs.10%) mainly due to pre-emptive factors such as technical difficulties and patient related factors (50% vs. 29%) and in lesser extent due to reactive factors (21%). Most indications for conversion described in literature are reactive in nature in contrast to this study. For example, obese patients were not always excluded for laparoscopy. A reactive conversion was required in only 3 patients.
Classical RPLND or RRRTM is associated with substantial morbidity. No significant difference was found in the perioperative complication rate between L-RRRTM and C-RRRTM (6% and 12%). In contrast, in an open and laparoscopic cohort, Nicolai et al. documented higher intraoperative laparoscopic complication rates of 37.9% vs. 21.8 % (NS)[22]. A smaller laparoscopic cohort showed a laparoscopic intraoperative morbidity of 33%[23]. The UMCG series showed that the postoperative morbidity was significantly lower in patients undergoing a successful L-RRRTM (12%) compared to those receiving the C-RRRTM including the LC-RRRTM group (35%). The higher postoperative complication rate in the LC-RRRTM and C-RRRTM groups is caused by the more extensive retroperitoneal disease in these patients and/or the anatomical location of the residual tumor mass. In contrast, Nicolai et al. documented no significant differences between the groups; 14% vs. 9%[22].

The median operative time in the present study was significantly shorter in the L-RRRTM group versus the LC-RRRTM and C-RRRTM group. This is to be expected since both groups had more extensive disease; the median residual tumor mass was 19 (range 5-57) mm in L-RRRTM group, 29 (range 16-70) mm in LC-RRRTM group,

Table 5.
Comparison series of laparoscopic RRRTM

Series	Year	N	Stage	RRTM size (cm)	Conversion rate N (%)	PC N (%)	RC N (%)	Peri-operative complications N (%)	Post-operative complications N (%)	Mean OR time (min)	Mean hospital stay (days)	Follow up mean (range) (months)	Recurrence N (%)
Rassweiler[19]	1996	8	2 IIB 7 IIC	-	6 (75)	5 (83%)	1 (17%)	0 (0)	1 (13)	357	7	27 (4-43)	none
Steiner[20]	2004	68	10 IIA 43 IIB 15 IIC	-	0			0 (0)	28 (17)	243	4	58 (3-121)	1 (1)
Albqami[14]	2005	59	43 IIB 16 IIC	-	0			9 (15)	11 (19)	234	4	53	1 (2)
Calestroupat[18]	2009	26	16 IIA/B 13 II C	3.4 (2-6)	5 (2.6)	1(20%)	4 (80%)	9 (35)	none	183	5	27 (14-36)	none
Busch[21]	2012	43	26 II 20 III	2.2	3 (6.5)	0	3 (100%)	21.7	-	212	6	30 (12-47)	4 (8.6)
Aufderkamm[24]	2014	19	5 IIA 7 IIB 5 IIC 2 III	3.87 (1.5-9.7)	0			0	2 (10.5)	212	6	18 (12-90)	0
Gaya[23]	2015	15	2 I 9 II 4 III	4.7	2 (13)	0	2 (100%)	5 (33)	-	294	5	29 (1-79)	none

Table 5. Continued

Series	Year	N	Stage	RRTM size (cm)	Conversion rate N (%)	PC N (%)	RC N (%)	Peri-operative complications N (%)	Post-operative complications N (%)	Mean OR time (min)	Mean hospital stay (days)	Follow up mean (range) (months)	Recurrence N (%)
Nicolai[22]	2016	67	14 IIA 41 IIB 7 IIC 5 III	27 (15-31)	3 (4.5)	2 (67%)	1 (33%)	1 (1.5)	3 (4.5)	234	3	21	none
Nakamura[25]	2016	14	14 IIA/B	25 (18-30)	0			0	7 (50)	439	1	36	none
UMCG series	2017	89	15 IIA 41 IIB 12 IIC 2 III 19 IV	19 (5-57)	14 (16%)	11 (78%)	3 (22%)	5 (6%)	9 (12%)	148	1	79 (7-144)	3 (4%)

and 42 (range 11-220) mm in the C-RRRTM group. In contrast, other more recent studies reported longer operative times for laparoscopic procedures of 234, 294, and 439 minutes[23-25]. Nicolai et al reported equivalent operative times (212 vs. 232 min, p = 0.3)[22]. A study originating from Japan reported not only longer operative times in the laparoscopic group, but also in the open group (439 vs. 408 minutes)[25].
As expected, the L-RRRTM group required a significantly shorter hospital stay compared to the LC-RRTM and C-RRRTM groups (medians of 1 day vs. 5 and 6 days; p <.001). In contrast to the short hospital stay for the laparoscopy patients in this series, the median hospital stay in other studies was longer after L-RRRTM, ranging from 3-7 days (Table 5). Nicolai et al. also compared the L-RRRTM group versus the C-RRRTM group and documented a median hospital stay of 6 vs. 11.5 days (p <.01)[22].

Thus far, there are no long-term outcome data in advanced nonseminomatous germ cell tumors comparing laparoscopic RRRTM to conventional RRRTM. After a median follow-up of 79 months, 27 patients (18%) developed recurrent disease; 19 in the initial C-RRRTM group (31%) and 8 in the initial L-RRRTM (9%): 4 in the final L-RRRTM group (5%) and 4 in the LC-RRRTM group (28%). The overall recurrence rate in the C-RRRTM, including the laparoscopy conversion patients, was not different from the initial C-RRRTM group (31%). The recurrences in the LC-RRRTM group were not related to the reason for the conversion; aortic injury, vena cava injury, and two technical difficulties due to extensive fibrosis. Other laparoscopic surgeries for resection of residual masses also showed low recurrence rates (Table 5). However, most reports consist of only small patient series and predominantly in patients with good prognosis disease and small residual tumor masses, with a limited follow-up duration[14,18-20].
When selecting patients for L-RRRTM, factors other than merely the size of the mass are important. Selection criteria are not absolute and these criteria are dynamic; first, in relation to developing skills and second, the anatomical site of the residual mass. Large residual masses greater than 5 cm might be eligible for a laparoscopic approach based on the laparoscopic experience of the surgical oncologist and the anatomical location.
Surgeons can now also perform robotic-assisted RRRTM[26,27]. Within a few years, robotic surgery might extend the indication for L-RRRTM, even for more challenging RRTM. L-RRRTM meets or exceeds the results from most open conventional surgeries and should always be considered as a viable alternative in the resection of residual tumor mass after cisplatin containing chemotherapy for locally advanced testicular cancer, offering less morbidity, a favorable cosmetic outcome for the patient, and a shorter hospital stay. The study showed that laparoscopic resection of RRTM in proper selected and well-defined patients is a feasible and oncologically safe procedure. Although a randomized trial comparing both treatment modalities is the gold standard to proof the superiority of this minimally invasive approach this will probably not performed. A multidisciplinary expert testicular cancer team with an experienced (oncological) laparoscopist is essential to discuss options with the patient.

In conclusion, with a robust sample size and a median follow-up duration of more than 6 years, this study confirms that laparoscopic resection of well-defined RRTM after cisplatin based combination chemotherapy for metastatic nonseminomatous testicular cancer is a feasible and safe surgical and oncological procedure, offering comparable oncological results as conventional surgery, with less morbidity, a shorter hospital stay, and an excellent cosmetic outcome for the patient with testicular cancer.

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Posterior Retroperitoneoscopic Resection of Recurrent Nonseminomatous Tumor Mass: A Report of the Surgical Procedure with a Review of the Literature

Abstract

Background

Treatment of stage II-IV nonseminomatous testicular germ cell tumors (NSTGCT) consists of cisplatin based combination chemotherapy and, when present, resection of residual retroperitoneal tumor mass (RRRTM) by conventional laparotomy or laparoscopy. In case of a retroperitoneal recurrence, a second conventional or laparoscopic procedure may be challenging.

Methods

A case of late relapse after prior conventional resection of a residual retroperitoneal tumor mass (RRTM) and the tailor made surgical management with a posterior retroperitoneoscopic resection is reported and the literature reviewed.

Results

The retroperitoneoscopic procedure was performed in a 26-year old male with a history of stage IIC NSTGCT, presenting with a late left sided retroperitoneal relapse, 6 years after initial treatment. The retroperitoneal cavity was entered through an alternative route by posterior retroperitoneoscopic resection of the RRTM. Histology showed mature teratoma. Postoperative course was uneventful and with a one year follow up the patient had no evidence of disease.

Conclusion

Reoperative surgery by a minimal invasive retroperitoneoscopic approach should be considered as an alternative approach for patients with a recurrent retroperitoneal tumor mass of a NSTGCT.

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BMJ Case Reports, submitted 2018

Introduction

Testicular germ cell tumors are rare tumors in the general population, but form the most common malignancy among men aged between 20-39 years[1]. In the last decades cisplatin based combination chemotherapy in the treatment of advanced nonseminomatous testicular germ cell tumor (NSTGCT) has impacted survival rates significantly, with an overall 10-year survival rate of up to 90%[2,3]. According to the prognostic classification, patients with advanced NSTGCT receive three or four courses of BEP (bleomycin, etoposide and cisplatin) after which restaging is performed with tumor marker analysis and computed tomography (CT) scanning of chest and abdomen. A wait and see policy is conducted in NSTGCT when tumor markers are normalized and no residual disease is detected (Figure 1).

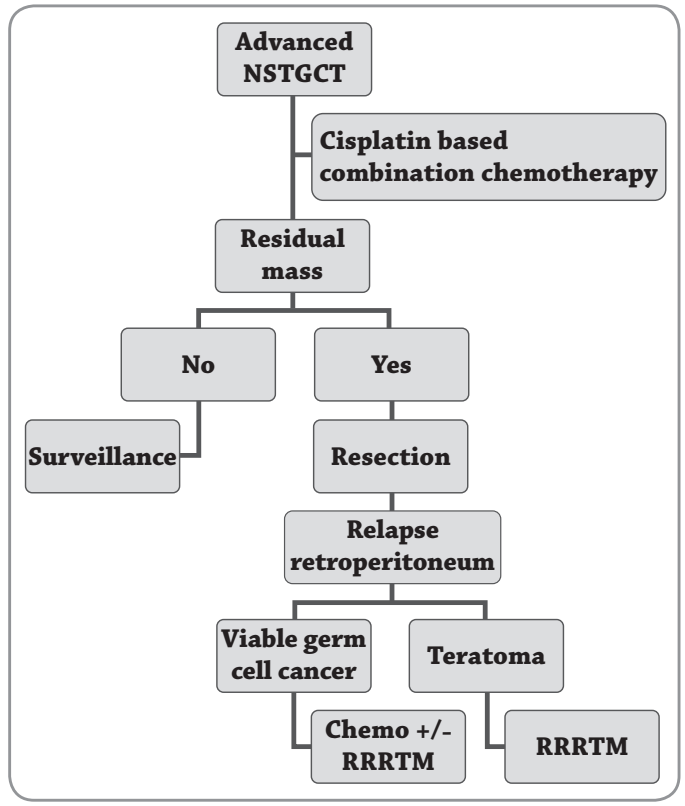

Figure 1
Summary of primary treatment of high stage NSTGCT.

Surgical resection is indicated in case of residual disease after chemotherapy. Most frequently this residual disease manifests as residual retroperitoneal tumor mass (RRTM) or in the lungs. The role of surgery in case of residual disease in NSTGCT treated with chemotherapy is to resect viable germ cell cancer and/or teratoma[4-7] usually via a classical approach performing a conventional open midline laparotomy. Laparoscopic surgery is mainly reserved for staging and treatment of low-stage disease[8,9], although at the UMCG low volume RRTM is also laparoscopically resected[10,11]. In 8 % of the NSTGCT patients that have been treated by combined therapy, e.g. chemotherapy and adjunctive surgery, recurrent disease was encountered[12,13]. Management is related mainly to the type of recurrence; growing teratoma, viable germ cell cancer or a secondary malignancy. In case of growing teratoma a resection is performed, whereas in case of presumed viable germ cell cancer the initial treatment will be chemotherapy followed by resection of residual tumor mass if indicated[15].
Relapses after prior conventional resections of RRTM are usually located in the retroperitoneum requiring extensive surgical exploration when the approach is conducted via laparotomy. An alternative surgical approach, the posterior retroperitoneoscopic resection (PRR), a surgical approach as used in the treatment of adrenal tumors, is described for the tailored resection of a recurrent RRTM with review of the current literature.

Case Representation

A 26 year old man was first diagnosed in 2008 with a left sided testicular tumor treated with inguinal orchiectomy. The resection specimen showed primarily embryonal carcinoma and teratoma. The disease was staged according to the Royal Marsden Classification system in stage IIC NSTGCT and IGCCCG (International Germ Cell Cancer Collaborative Group) intermediate risk group[2]. The patient received 4 courses of cisplatin based combination chemotherapy (BEP). Restaging procedures revealed normalised alpha-fetoprotein (AFP) and a normal betachoriongonadotropin <1 U/L. Furthermore, CT scan of thorax and abdomen showed a left sided retroperitoneal paraaortic tumor mass, situated caudally of the renal hilus, measuring 6x7 cm (prior 5x5cm) and a second retroperitoneal tumor mass situated interaortocaval measuring 1.7x1.9 cm (prior 2.6x3cm) (Figure 2a). Subsequently, the patient underwent a conventional midline laparotomy to resect the residual retroperitoneal tumor masses. Histopathology results showed a complete (R0) resection and surgical specimens consisted of fibrotic tissue and teratoma with mature and immature compounds. Normally, follow up is performed according to the ESMO guidelines with testicular tumor markers and abdominal and chest CT[16]. However there was a lack of patient adherence to the follow up schedule due to relocation abroad. He presented himself 6 years later with a request to resume follow up. There were no presenting symptoms at that time. Unfortunately a retroperitoneal recurrence located at the left retrocrural space with a diameter of 17 mm (Figure 2b) with normal tumor markers was diagnosed 87 months after initial resection of RRTM. The recurrence, diagnosed to be suggestive for a growing teratoma, was located far from the initial residual disease location and previous operative resection area. The patient was discussed in the weekly multidisciplinary tumor board and it was decided to implement a posterior retroperitoneoscopic resection of the recurrent disease. The goal was to select the procedure with the highest chance of a complete resection of this late relapse with a minimal treatment related morbidity and a fast recovery and without surgically dealing with scarred tissue and adhesions of a prior operation field.

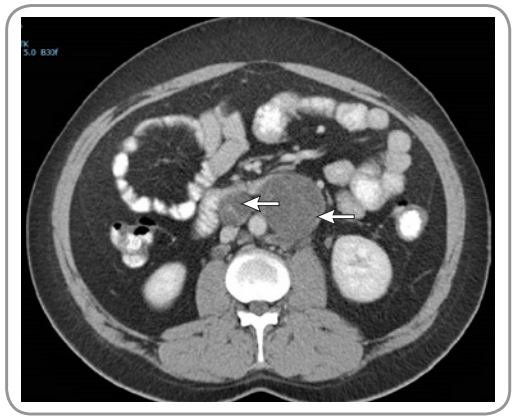

Figure 2a.
CT scan showing 2 retroperitoneal tumor masses.

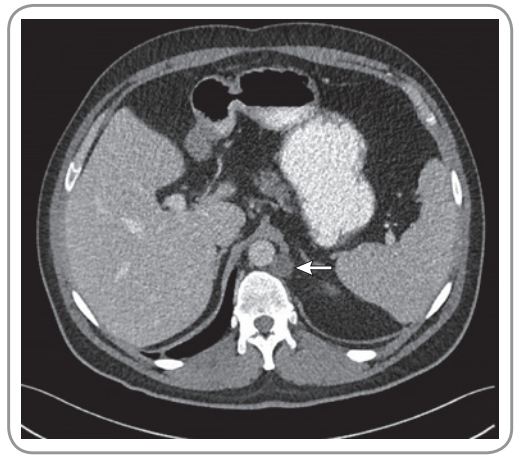

Figure 2b.
CT scan showing retroperitoneal turmor recurrence.

Surgical Procedure and Postoperative Course

Two surgical oncologists performed the surgical procedure with laparoscopic experience in performing posterior retroperitoneoscopic adrenalectomy (PRA)[17-19]. The retroperitoneoscopic procedure was performed with the patient in the prone

position and the surgeon positioned ipsilateral to the tumor, with the assistant at the opposite side holding the camera. Two video monitors were placed near the patient's head to provide a comfortable view for both surgeons.

The first part of the surgery involved introduction and developing sufficient retroperitoneal space with blunt dissection and carbon dioxide instillation. A first incision was made below the tip of the 12th rib of about 1.5 cm, eventually serving as a camera port and the second port was then placed without camera view on the index finger (Figure 3). Pneumoperitoneum was created with a high pressure of 25mm Hg. After having created enough working space a third 10 mm port was placed under camera view. Firstly, the left renal hilus was exposed mobilizing the left kidney from its surroundings. After mobilizing the kidney laterally, the tumor mass then could be identified. Resection of the tumor was performed according to the same oncological principles as in a conventional resection of a RRTM excising only the visible abnormal retroperitoneal tumor mass, as previously described[10,11]. Proximal dissection was carefully performed around the left renal artery and vein. The tumor was gently separated off the aorta by blunt and sharp dissection. Finally, the resected retroperitoneal tumor mass was placed in an endoscopy bag and extracted from the extraperitoneal cavity through the first incision site. Procedure time was 120 minutes. No intra operative complications occurred during the procedure.

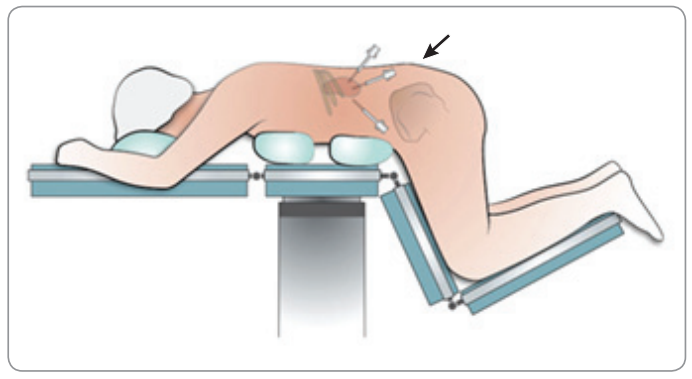

Figure 3.
Schematic positioning of a patient in the prone position during the retroperitoneoscopic procedure to excise the RRTM.
**Arrow is directed at the port positions; in the middle the camera port is shown.*

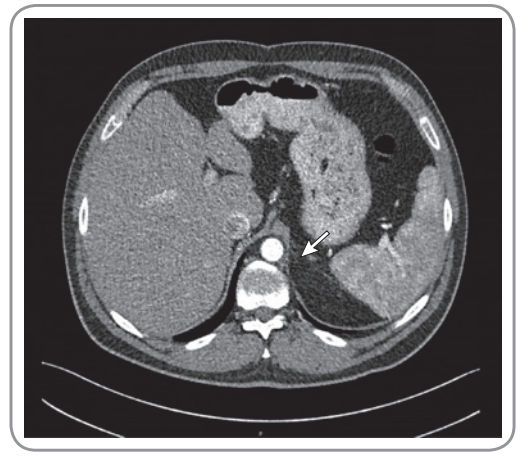

Figure 4.
*CT scan postoperatively. *Arrow is directed at the adrenal which was not damaged during procedure.*

The postoperative course was uneventful. The patient was discharged the next day. The resection specimen showed a Ro resection of a retroperitoneal tumor mass with remnants of mature teratoma. During the following 12 months of follow-up the patient had no evidence of disease with normal tumor markers and a normal abdominal and chest CT (Figure 4).

Discussion

Based on the current literature roughly 3-23% of the advanced NSTGCT patients develop a recurrence after previous standard cisplatin based combination chemotherapy with or without resection of residual disease. Surgical resection of residual disease is required by either a modified retroperitoneal lymph node dissection (RPLND), or nerve sparing RPLND, or only resection of residual retroperitoneal tumor mass (RRRTM). Extra template disease in NSTGCT, occurring outside these resection templates and the corresponding histologic distribution is nearly identical to the histologic distribution within the surgical templates with initial RPLND as well as post-chemotherapy RPLNDs[20,21]. Twenty to thirty percent of patients with advanced NSTGCTs relapse or fail to achieve a complete response with cisplatin based combination chemotherapy[22-24]. This also depends on the prognostic factor-based staging system of the International Germ Cell Cancer Collaborative Group: good, intermediate or poor risk group[2].

At the UMCG the current relapse rate in advanced NSTGCT patients treated with cisplatin based combination chemotherapy and, if indicated, resection of all visible residual disease, is 18 %[11]. Histology shows that teratoma is often present in late relapses and reoperative surgery[11]. Since teratoma's are unresponsive to both chemotherapy and radiotherapy, complete resection of all residual tumor masses is an essential part of the combined treatment of NSTGCTs. Also mature

teratoma can dedifferentiate into malignant tissue with either germ cell or non-germ cell elements[14]. Chemotherapy does not compensate for suboptimal surgical resections of residual disease without viable carcinoma.
Since these relapses of the retroperitoneum tend to be chemoresistent, a selection of patients with anatomically well-defined retroperitoneal disease require reoperative retroperitoneal surgery in a so-called curative setting. These redo surgeries are accompanied by significant morbidity and risks and can be technically challenging procedures because of postchemotherapy desmoplastic reaction and annihilated and scarred surgical tissue planes with dense adhesions due to prior surgery[25-27]. All of these factors increase the possibility of adjunctive resections such as a nephrectomy, resection of visceral structures and obliged vascular surgery. Long term survival varies from 63% to 91.3% and is therefore worse than patients requiring postchemotherapy resection of residual disease alone[13,27]. Factors such as histological type of the recurrence, the possibility of salvage chemotherapy, the anatomical site of the recurrence and the experience of the surgical oncologist can explain this wide variance in survival rates. Literature concerning reoperative retroperitoneal surgery in NSTGCTs is limited, although surgery is critical in achieving durable complete remissions.
Understanding the typical dissemination patterns of this disease is essential for the surgical oncologist. Lymphatic drainage of the retroperitoneum plays a major role in determining this pattern, with the paraaortic and paracaval lymphatics draining behind the crura of the diaphragm. Majority of retroperitoneal recurrences are located in the paraaortic mostly left-sided and interaortocaval regions, making reoperative retroperitoneal surgery challenging[27]. Patients who are candidates for resection of recurrent disease should first undergo accurate staging with CT of abdomen and chest, sometimes MRI or even PET CT might be required. By using imaging we want to exclude patients with extra-abdominal and non-retroperitoneal disease that cannot be surgically cured. The goal of surgery should always be a Ro resection meaning to resect all abnormal tissue. Pedrosa et al. declared 27% of NSTGCTs patients with a relapse even unresectable after attempting redo surgery[27].
In the current patient, technical challenges were taken into account upfront. The residual tumor mass was situated at a difficult and challenging retrocrural location. With the experience and confidence gained from the PRA, the decision was made in the tumor board conference to perform a PRR instead of an approach via conventional midline laparotomy. This way, the previous transabdomininal surgical route was bypassed and surgery could be performed partially in a “virgin” territory creating significantly less morbidity. The hospital stay was one day.

Today still most of the surgical resections for recurrent NSTGCTs are performed through a conventional midline or transverse exposure. In almost all cases a laparoscopic procedure is not suitable. The retroperitoneoscopic technique as used for adrenalectomy might be an alternative option. However, PRR requires a substantial learning time and is technically challenging[17-19].

Conclusion

In case of relapse after resection of residual retroperitoneal tumor mass and previous cisplatin based combination chemotherapy for NSTGCTs, alternative surgical strategies may be discussed in the multidisciplinary tumor conference. When anatomically feasible, PRR can avoid the impact of extended conventional surgery or relaparoscopy on the abdominal organs creating less morbidity with respect to bowel and pulmonary function.

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Future Perspectives

Future Perspectives

Today, with the high cure rates presented for disseminated testicular cancer (TC) after treatment with cisplatin based combination chemotherapy, higher than for any other metastasized cancer treated with chemotherapy, it is hard to imagine how these results can be improved beyond the current results. This success comes at the price of late- and long-term toxicity caused by the initial treatment. The impact of the burden of these late- and long-term effects becomes increasingly clear. Hence, there is a noticeable shift in the focus of testicular cancer research aiming to reduce or prevent treatment related morbidity. Reducing morbidity of treatment also starts with reducing patient and doctor delay when diagnosing testicular cancer. Today given the increasing incidence of TC, it is important to keep the focus on better education to the general public, e.g. adolescents (and their parents) and young adults, as well as physicians to increase awareness and knowledge about testicular cancer and subsequently decreasing delay. Research has shown that there is a trend in reduction of tumor size at presentation through the years and men presenting with TC are younger of age at first presentation[1]. Therefore, promotion of regular periodic testicular self-examination and public education should remain important initiatives. Health care providers who aim to develop education programs to increase TC awareness in young men should take into account that men who feel embarrassed about scrotal changes and lower educated men may benefit most from their programs.

When evaluating retroperitoneal residual tumor masses after completion of cisplatin based combination chemotherapy in patients with a biochemical complete remission, it is not possible to make the distinction between malignant and non-malignant disease. To date resection of these masses is still seen as the most accurate staging method and treatment, since 40-45% of these masses contain teratoma and 10-15% viable germ cell tumor. About 40-50% of patients who have necrotic and/or fibrotic residual masses, are unnecessarily exposed to surgery and gain no benefit from resection of these masses. Diagnostic workup of patients with residual masses remains a clinical challenge and more research is needed to determine accurate markers to predict viable residual disease. There is no diagnostic imaging tool that can help discriminate between viable germ cell cancer, mature teratoma or fibrosis. In this thesis one focus was on investigating and exploring a new modality, in specific volumetric analysis, which can be applied to monitor treatment response for advanced NSTGCT and help distinguish responders from non-responders. The future usage of volumetric analysis in retroperitoneal lymph

node masses in advanced NSTGCT can be promising, but more research is needed to define its merits in this specific patient category.

Advances made in molecular medicine, specifically in microRNA (miRNA) biology since the discovery in 1993[2] are promising and have markedly benefited TGCT research[3-6]. These miRNAs have gained importance because of specific characteristics, such as high stability in body fluids and easy detection, allowing miRNAs to act as novel biomarkers. In TGCT research the miRNA-371-3 cluster is of specific interest being overexpressed in malignant TGCTs. A first report of this important finding was published in 2011 with a decline of serum miRNA levels after treatment of a patient with paediatric TGCT[7]. More recently Leão and colleagues analyzed serum levels of three miRNAs (miR-371a-3p,miR-373-3p, and miR-367-3p) in patients who were treated for advanced TGCT[6]. These measurements were evaluated in relation to clinical characteristics and serum tumor markers and also tumor histology after therapy. In this study it was concluded that miR-371a-3p serum level seemed to be a useful biomarker in TGCTs predicting the presence of viable residual disease after treatment[6]. Although more research is needed, for example with regard to the specificity of miR-371a-3p as a biomarker, the potential of using miR-371a-3p as a new additive biomarker could have a positive influence on the management of advanced TGCTs. Currently such fundamental research is being performed at our center in a cohort of testicular cancer patients with recurrent or refractory disease after cisplatin based combination chemotherapy. This line of research could result in a lower frequency of routine follow up CT scans of chest and abdomen and therefore reduced radiation burden and more importantly a specific group of patients could be identified in which comfortably a wait-and-see policy can be executed and unnecessary surgery can be avoided.

In this thesis the main focus has been placed on minimally invasive procedures to resect retroperitoneal residual tumor masses. Morbidity associated with a conventional midline laparotomy is high and therefore even in advanced stages, laparoscopic procedures are continuously more performed. In the nearby future other minimally invasive procedures, such as the robot-assisted retroperitoneal lymph node dissection will also be more frequently used. With the availability of the Da Vinci Robot at the UMCG in 2018, this robotic technique to resect residual retroperitoneal tumor masses will be explored in the treatment of disseminated testicular cancer. Advantages for patients are thought to be equal to laparoscopic surgery with less morbidity compared to a laparotomy. Also there are indications that improved visualization and dexterity over conventional laparoscopy, can lead to significantly reduced morbidity for the TC patient[8]. In times where surgeons are facing an ergonomic crisis, where increasingly complex laparoscopic procedures are executed, another important advantage is that robotic surgery also offers optimal ergonomics for the operating surgical oncologist.

Over the last decades significant strides have been made in testicular cancer research, and small steps but equally important steps will follow. Fine tuning management regarding the treatment in testicular cancer should always continue since although rare, testicular cancer overwhelmingly occurs in young men and is the most common cancer in young men. Even in the future, treatment in testicular cancer should serve as an example for the treatment of other cancers. Another important part of the current and future research at the UMCG is to improve insight in the pathogenesis of short- and long-term treatment related side effects and how to manage them. Several projects concern the identification of TC patients who are more susceptible to treatment related morbidity. This treatment related morbidity in TC survivors resemble the accelerated aging phenotype. TC patients at a high risk for late effects might benefit from intervention strategies such as lifestyle and physical activity programs. Intervention trials to address these issues are currently performed at the UMCG. Another important issue is how to take care of the increasing number of TC survivors. Just recently a shared care survivorship program for testicular cancer survivors, in which follow-up was done by the oncologist together with the patient and his primary care physician, was completed and appeared to be safe[9]. For the nearby future such developments are of importance for the increasing number of testicular cancer survivors. The ultimate goal remains to improve the short and long-term outcome of patients with testicular cancer.

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8

Summary & Samenvatting

Summary

Treatment of testicular cancer (TC) represents a success story in oncology since it can be stated that an incurable disease transformed to a curable one. Nowadays it is hard to imagine that times existed when so many young men died of testicular cancer with an overall cure rate of 25 %. This was the case in the early seventies before the cisplatin era commenced. The results of the three drug regimen introduced by Einhorn and colleagues were astonishing, resulting in survival rates up to 80% and nowadays even up to 95%, the highest success rate of any type of cancer. After the improved results of chemotherapy, surgical advancements followed in the 1980s, describing the nerve-sparing retroperitoneal lymph node dissection (RPLND), aiming to reduce surgical associated morbidity, e.g. preserving postoperative ejaculation. In the field of surgery certainly advancement has not stopped, leading to minimally invasive procedures.
Nowadays attention has shifted to further refinement of different aspects in testicular cancer treatment and reducing the “burden of treatment” for patients, such as reducing toxicity, short- and long-term morbidity of treatment regimens and improving non-cancer related & cosmetic results related to surgery.
Testicular cancer research has revealed major milestones in the past five decades. Still more research is needed, since new questions are always raised in science, and answering one question creates more questions. These new scientific questions also need to be answered, to further stimulate advancement in science. This thesis focused on various aspects of new treatment strategies in the staging and surgical treatment of nonseminomatous germ cell tumors (NSTGCT). Generating new data by research and therefore improving knowledge will hopefully continue to improve current medical care in testicular cancer patients and their respective families.

In the introduction of this thesis in **Chapter 1** a general introduction about testicular germ cell tumors is given with an up-to-date overview on several epidemiological, etiological and clinical aspects. Contemporary practice in the management and treatment of testicular cancer is discussed, which also contains the World Health Organization histological classification system and the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification system both important in drawing up a treatment plan. Surgical treatment in advanced NSTGCT after cisplatin based combination chemotherapy and follow up after adjunctive surgery aiming to detect disease relapse are described.

Before treatment of testicular cancer can be commenced, patients have to be referred to a surgeon or an urologist. In **Chapter 2** factors influencing patient and doctor delay in the diagnosis of TC are discussed. Researchers report many men who suspect having TC that wait several weeks, months, or even years before first consulting a doctor. These men explain having feelings of embarrassment, and losing their masculinity. Delay in this group of patients is frustrating. However, treatment delay can also be caused by physicians. Delay can have an impact on survival, additional treatment may be required and morbidity is unnecessarily increased in this group of young men. In this chapter a study is presented related to delay aiming to get insight into the length of patient and doctor delay in the diagnosis of testicular cancer and to examine factors associated with delay in diagnosis of testicular cancer. Median patient reported delay was 30 days with a wide range from 1 day up to 365 days. A significant association was found as expected between patient delay and TC tumor stage. Also, lower educated men and men embarrassed about their scrotal change reported longer patient delay. Factors such as age, marital status, TC awareness, warning signals, and perceived limitations due to TC were not associated with patient delay. Median patient reported time from general practitioner until specialist visit was 7 days with a wide range of 0 to 240 days. Six patients never reported a scrotal change. Of the 54 patients reporting a testicular change, 29 (54%) patients were initially not diagnosed as having a, for testicular cancer suspected scrotal abnormality, leading to a median doctor's delay of 14 (1-240) days, which was longer (p <.001) than in the 25 (46%) patients whose general practitioner (GP) suspected the presence of a testicular tumor (median doctor delay 1; range 0-7 days).
In conclusion, high variation in patient and doctor delay was found. Most important risk variables for longer patient delay were embarrassment and lower education and most important risk variable in doctor delay was 'not suspecting a malignant tumor'.

Adequate staging is fundamental in determining the prognosis and the optimal treatment strategy for each individual patient. Computed Tomography (CT) of chest and abdomen serves as the main diagnostic tool to determine pre- and post-chemotherapy tumor deposit size, allowing evaluation of treatment response and guiding the decision to perform resection of residual retroperitoneal tumor mass (RRRTM). Optimal disease management is based on reliable and reproducible lesion measurement. Volumetric analysis is a new promising technique to measure a therapeutic response especially for lung and liver lesions, which can also be used to measure response of retroperitoneal lymph nodes of testicular cancer after chemotherapy. In **Chapter 3** a pilot study is described which was executed at the UMCG to assess the suitability and reproducibility of semi-automated volumetric analysis when applied to retroperitoneal lymph nodes in patients with disseminated NSTGCTs, compared to 2 dimensional measurements using computerized volumetric analysis software. Retroperitoneal lymph node metastases of 21 patients were studied with a CT scan of chest and abdomen before and after cisplatin based combination chemotherapy. Tumor assessment was performed independently using computerized volumetric analysis by three readers; a surgical resident, a radiological technician and a radiologist, and manual measurement according to the RECIST criteria (version 1.1). In both measurement modalities assessment of intra observer and inter observer variance proved non-significant. In particularly all correlation values for the volumetric analysis were >.99 per observer and between observers. Minimal bias in agreement for manual as well as volumetric analysis was found. Therefore, it can be concluded that volumetric measurement appears to be a reliable, reproducible method to measure initial tumor volume of retroperitoneal lymph nodes metastases of testicular cancer before and after chemotherapy, even when performed by experienced non-radiologists in the clinical setting.

In **Chapters 4** and **5** the feasibility of laparoscopic resection of residual masses in the retroperitoneum after cisplatin based combination chemotherapy for advanced nonseminomatous testicular cancer is described. In **Chapter 4** a first report, a pilot study, is presented, on the UMCG experience with respect to the current approach in the surgical treatment of residual retroperitoneal disease after combination chemotherapy in advanced NSTGCTs. In this pilot study 29 patients out of 79 consecutive patients with disseminated NSTGCTs treated with cisplatin based combination chemotherapy were found eligible for laparoscopic resection of retroperitoneal residual tumor mass (L-RRRTM). Selection criteria for L-RRRTM first mentioned in this study were patients with a residual retroperitoneal tumor mass less than 5 cm and located ventrally or laterally from the aorta or the vena cava. In 25 patients (86%) L-RRRTM was performed successfully. Only four patients (14%) required a conversion of the laparoscopic procedure; three laparotomies (in 2 patients due to bleeding and in one patient due to obesity and therefore inadequate exposure) and one hand-assisted procedure (due to extreme obesity). After a median follow up of 47 months, one patient experienced a relapse.
Laparoscopic retroperitoneal nerve preserving lymph node dissection has already been used in the treatment for testicular cancer in stage I/II disease for over a decade. The UMCG was one of the first testicular cancer centers in the world who introduced this technique as an adjunctive treatment for more advanced disease stages in testicular cancer, e.g. laparoscopic resection of residual retroperitoneal

disease after cisplatin based combination chemotherapy in NSTGCTs. In the following years the laparoscopic series expanded consisting of 75 patients, resulting in one of the largest laparoscopy series in the current literature with respect to resection of residual retroperitoneal disease in NSTGCTs after cisplatin based combination chemotherapy. In **Chapter 5**, a series of 150 patients with residual retroperitoneal disease after completion of chemotherapy is described; results of 75 patients receiving adjunctive laparoscopic surgery (L-RRRTM) were compared with a group of 75 retrospectively selected patients who underwent conventional midline laparotomy. L-RRRTM primarily was scheduled in 89 patients with a median residual tumor diameter of 20 (range 5-70) mm, however conversion was necessary in 14 patients (15%). Perioperative complications occurred equally in the L-RRRTM and conventional RRRTM (C-RRRTM) group. As to be expected median duration of C-RRRTM was longer than operative time in L-RRRTM (median 221 versus 146 minutes, p <.001). In the L-RRRTM group 9/75 patients (12%) had postoperative complications versus 26/75 patients in the C-RRRTM group (thus including conversions) (35%, p <.001). Median postoperative stay in the L-RRRTM group was significantly shorter in the L-RRRTM group versus the C-RRRTM group (median of 1 day vs. 5 days, p <.001). A median follow-up of 79 (2-144) months was achieved. In this period 4 (5%) patients in the L-RRRTM group had a recurrence versus 23 (31%) in the C-RRRTM group (p <.001). The study design being merely a descriptive study makes it difficult to compare the two modes of resection. It can be concluded that the laparoscopic procedure is feasible and appears also oncologically to be safe in selected patients resulting in shorter hospital stay and good oncological and excellent cosmetic results. Long-term follow up has been established in a large cohort of patients. With growing experience over the years we can state that when selecting patients for L-RRRTM, factors other than merely the size of the mass are important. These criteria are dynamic; first, in relation to developing skills of the surgical oncologists and second, the anatomical site of the residual retroperitoneal tumor mass which is evaluated per case. Performing a conversion when required should patient wise not be considered a “complication”. Considering the advantages of a minimally invasive procedure, it is best to offer a patient a laparoscopic procedure above a conventional laparotomy when evaluated as being a possibility based on solid arguments and experience. When laparoscopy is successful, the young testicular cancer patient leaves the hospital with three minimal visible scars! No middle scar, remaining as the surgical tattoo of previous testicular cancer treatment. Additional long-term outcome data needs to be awaited.

The discussion with respect to minimal invasive procedures has always been clouded by controversies surrounding the care of patients with disseminated nonseminomatous testicular germ cell tumors with regard to the extent of resection. In the United States of America a strong urological surgical tradition directs treatment into a more aggressive surgical approach whereas in Europe a more conservative surgical approach is generally favored only completely resecting the ‘visible residual masses’. This discussion surrounding the optimal management of post chemotherapy residual retroperitoneal tumor masses is exacerbated by a lack of comparative and randomized data, and is influenced by geographic different surgical choices made in treatment of patients with advanced NSTGCTs. Furthermore, the results of the study presented in **Chapter 5** are based on the Dutch and European testicular cancer treatment guidelines in which only the residual retroperitoneal disease is resected to remove residual viable germ cell cancer and teratoma to prevent a growing teratoma syndrome and development of non-germ cell malignancies. This approach has excellent survival rates of over 80-90%. Also, the principles of resection in the laparoscopic adjunctive oncologic surgical approach in the combined treatment of advanced nonseminomatous testicular cancer are equal to that of conventional surgery for disseminated testicular cancer..

In **Chapter 6** a novel alternative approach for resection of a residual mass in nonseminomatous germ cell tumors is described. This approach may be considered in a subset of patients with unresected disease or a recurrence in the retroperitoneum in the postchemotherapy surgical setting after prior retroperitoneal lymph node dissection (RPLND) or RRRTM. With the confidence and experience gained from adrenal surgery, the Posterior Retroperitoneoscopic Resection (PRR) was performed on a patient with a nonseminomatous germ cell tumor relapse located at the left retrocrural space. Postoperative recovery was uneventful and hospital stay one day. Redo surgeries are accompanied by significant morbidity and risks and can be technically challenging procedures because of postchemotherapy desmoplastic reaction and annihilated surgical tissue planes and dense adhesions due to prior surgery. Therefore this novel approach, the PRR, can be considered when defining a treatment plan for an individual patient. Although it may not be required often, it should be present in the palette of surgical choices that can be made for testicular cancer patients with residual (recurrent) disease after previous combination chemotherapy.

At the UMCG, a tertiary referral center for patients with TC, considerable institutional research has already been published on the subject covering many aspects of TC. This thesis is one of many in this extensive line of research tradition. Therefore it was felt necessary to provide insight into this specific academic history and an **Appendix** was added to this thesis. In this additional Chapter, a detailed historical overview of the testicular cancer treatment at the UMCG is presented as it was performed at the Department of Surgical Oncology from the sixties of the last century until now covering surgical and non-surgical modalities of treatment. Also the transformation in the treatment of TC over the past decades into a multimodality treatment in which today over eight medical disciplines (surgeons, urologists, medical oncologists, radiation oncologists, pathologists, radiologists, nuclear medicine physicians, geneticist, psychologists) and basic researchers are involved, is described.

Samenvatting

De behandeling van testiskanker kan een succesverhaal in de oncologie worden genoemd: de ooit ongeneeslijke ziekte is een geneeslijke ziekte geworden. Het is tegenwoordig nauwelijks nog voor te stellen dat er tijden zijn geweest waarin zoveel jonge mannen overleden aan testiskanker, met een overall genezingsratio van 25%. Dit was het geval in de vroege jaren zeventig, voor aanvang van het cisplatinetijdperk. De resultaten van het door Einhorn en collega's geïntroduceerde driedrugregime waren opzienbarend en resulteerden in overlevingsratio's van tot wel 80% en tegenwoordig zelfs 95%, de hoogste succesratio van alle soorten kanker. Na de verbeterde resultaten van chemotherapie volgde in de jaren tachtig de chirurgische vooruitgang met zenuwsparende retroperitoneale lymfeklierdissectie (RPLND), bedoeld om de chirurgie gerelateerde morbiditeit te reduceren, bijvoorbeeld door behoud van postoperatieve ejaculatie. Op chirurgisch gebied is de vooruitgang hierna zeker niet gestopt, met als gevolg de ontwikkeling van minder invasieve procedures.
Inmiddels is de aandacht verschoven naar verdere verfijning van verschillende aspecten in de behandeling van testiskanker en reductie van de 'behandelingslast' voor patiënten, zoals het reduceren van toxiciteit, morbiditeit van behandelingsregimes op de lange en korte termijn en verbetering van niet-kanker gerelateerde en kosmetische resultaten gerelateerd aan chirurgische ingrepen.
Testiskankeronderzoek heeft in de afgelopen vijftig jaar heel wat mijlpalen opgeleverd. Er is nog altijd meer onderzoek nodig, in de wetenschap komen nu eenmaal altijd weer nieuwe vragen op en een beantwoorde vraag creëert weer nieuwe vragen. Ook deze nieuwe wetenschappelijke vragen moeten beantwoord worden om verdere vooruitgang in de wetenschap te stimuleren. Dit proefschrift focust op verschillende aspecten van nieuwe behandelstrategieën op het gebied van stadiëring en chirurgische behandeling van non-seminomateuze kiemceltumoren (NSTGCT's). Door het genereren van nieuwe data uit onderzoek en de daaruit voortvloeiende kennis zal de huidige medische zorg hopelijk blijven verbeteren voor testiskankerpatiënten en hun naasten.

In de introductie van dit proefschrift in **Hoofdstuk 1** wordt een algemene inleiding gegeven over kiemceltumoren van de testis, met een up-to-date overzicht van verschillende epidemiologische, etiologische en klinische aspecten. Er wordt ingegaan op moderne praktijken in de medische zog en de behandeling van testiskanker, waaronder het histologische classificatiesysteem van de Wereldgezondheidsorganisatie (WHO) en het prognostische classificatiesysteem van de Inter-

national Germ Cell Cancer Collaborative Group (IGCCCG), beide van belang bij het opzetten van een behandelplan. Ten slotte volgt een beschrijving van de chirurgische behandeling in NSTGCT's in een gevorderd stadium na een cisplatine bevattende combinatiechemotherapie en follow-up na adjuvante behandeling om relaps van de aandoening te detecteren.

Voordat kan worden begonnen met de behandeling van testiskanker moeten patiënten worden doorverwezen naar een chirurg of een uroloog. In **Hoofdstuk 2** worden factoren besproken die van invloed zijn op behandelvertraging door patiënt en arts bij de diagnose van testiskanker. Onderzoekers melden dat mannen die vermoeden testiskanker te hebben, vaak meerdere weken, maanden, soms zelfs jaren wachten voordat ze voor het eerst een arts consulteren. Als reden hiervoor noemen deze mannen gevoelens van schaamte en verlies van hun mannelijkheid. Vertraging bij deze groep patiënten is frustrerend. Behandelvertraging kan echter ook worden veroorzaakt door artsen. Vertraging kan invloed hebben op de overlevingskansen, kan aanvullende behandeling noodzakelijk maken en de morbiditeit bij deze groep jonge mannen onnodig verhogen. In dit hoofdstuk wordt een studie gepresenteerd die zich bezighoudt met deze vertraging, met als doel inzicht te krijgen in de lengte van de door patiënt of arts veroorzaakte vertraging bij de diagnose van testiskanker en te onderzoeken welke factoren geassocieerd worden met een vertraagde diagnose van testiskanker. De gerapporteerde gemiddelde patiëntvertraging bedroeg 30 dagen, met een groot bereik van 1 dag tot 365 dagen. Zoals verwacht, werd een significant verband gevonden tussen patiëntvertraging en tumorstadium van de testiskanker. Ook bleken mannen met een lager opleidingsniveau en mannen die zich schaamden voor de verandering aan hun scrotum langere patiëntvertraging te vertonen. Factoren zoals leeftijd, burgerlijke staat, kennis van testiskanker, waarschuwingssignalen en beperkingen die werden ervaren als gevolg van de testiskanker worden niet met patiëntvertraging geassocieerd. De gemiddelde door de patiënten gerapporteerde tijd tussen bezoek aan huisarts en bezoek aan specialist was 7 dagen, met een bereik van 0 tot 240 dagen. Zes patiënten hadden een verandering aan het scrotum helemaal niet gemeld. Van de 54 patiënten die een verandering aan de testis wel hadden gemeld, werden 29 (54%) patiënten aanvankelijk niet gediagnosticeerd met een voor testiskanker verdachte scrotale afwijking, wat leidde tot een gemiddelde artsvertraging van 14 (1-240) dagen, wat langer was (p <.001) dan bij de 25 (46%) patiënten bij wie de huisarts wel de aanwezigheid van een testistumor vermoedde (gemiddelde artsvertraging 1; bereik 0-7 dagen).
Concluderend, werd er een hoge variatie in patiënt- en artsvertraging gevonden. De belangrijkste risicovariabelen voor langere patiëntvertraging waren schaamte en een lager opleidingsniveau, de belangrijkste risicovariabele bij artsvertraging was 'geen vermoeden van een kwaadaardige tumor'.

Adequate stadiëring is fundamenteel bij het vaststellen van de prognose en optimale behandelstrategie voor iedere individuele patiënt. Computertomografie (CT) van borst en buik dient als belangrijkste diagnostische 'tool' om de pre- en postchemotherapeutische omvang van tumordeposities te bepalen. Op grond hiervan kan een evaluatie van de behandelrespons plaatsvinden en kan al dan niet worden besloten tot het verwijderen van retroperitoneale restmassa (RRRTM). Optimale ziekte behandeling is gebaseerd op betrouwbare en reproduceerbare laesiemeting. Volumetrische analyse is een nieuwe, veelbelovende techniek voor het meten van therapeutische respons, met name bij long- en leverlaesies, maar kan ook gebruikt worden om de respons van retroperitoneale lymfeklieren bij testiskanker na chemotherapie te meten. In **Hoofdstuk 3** wordt een pilotstudie beschreven die is uitgevoerd aan het UMCG om de geschiktheid en reproduceerbaarheid van semiautomatische volumetrische analyse te bepalen indien toegepast op retroperitoneale lymfeklieren bij patiënten met uitgezaaide NSTGCT's in vergelijking met tweedimensionale metingen met gebruik van gecomputeriseerde software voor volumetrische analyse. Retroperitoneale lymfekliermetastases van 21 patiënten werden bestudeerd aan de hand van een CT-scan van borst en buik voor en na cisplatine bevattende combinatiechemotherapie. Tumorbeoordeling werd onafhankelijk uitgevoerd met gebruik van gecomputeriseerde volumetrische analyse door drie lezers: een chirurg in opleiding, een radiologisch laborant en een radioloog, en handmatige meting volgens de criteria van RECIST (versie 1.1). In beide meetmodaliteiten bleek de mate van intra- en interbeoordelaarsvariatie verwaarloosbaar. Met name alle correlatiewaarden voor de volumetrische analyse waren >.99 per beoordelaar en tussen beoordelaars. Een minimale bias in zowel handmatige als volumetrische analyse werd aangetroffen. Er kan daarom worden geconcludeerd dat volumetrische meting een betrouwbare, reproduceerbare methode lijkt om het initiële tumorvolume van retroperitoneale lymfekliermetastases bij testiskanker voor en na chemotherapie te meten, zelfs wanneer uitgevoerd door ervaren niet-radiologen in een klinische setting.

In **Hoofdstuk 4** en **5** wordt de haalbaarheid van laparoscopische resectie van restmassa in het retroperitoneum na cisplatine bevattende combinatiechemotherapie voor non-seminomateuze testiskanker in een gevorderd stadium beschreven. In **Hoofdstuk 4** wordt een eerste rapport gepresenteerd, een pilotstudie, over de ervaring van het UMCG met betrekking tot de huidige aanpak bij de chirurgische behandeling van retroperitoneale restziekte na combinatie-

chemotherapie bij NSTGCT's in een gevorderd stadium. In deze pilotstudie bleek dat van 79 achtereenvolgende patiënten met uitgezaaide NSTGCT's die behandeld waren met cisplatine bevattende combinatiechemotherapie, 29 patiënten in aanmerking kwamen voor laparoscopische resectie van retroperitoneale restmassa (L-RRRTM). Selectiecriteria voor een L-RRRTM die eerst genoemd worden in deze studie waren patiënten met een retroperitoneale restmassa kleiner dan 5 cm, gelokaliseerd ventraal of lateraal van de aorta of de vena cava. Bij 25 patiënten (86%) werd met succes een L-RRRTM uitgevoerd. Slechts vier patiënten (14%) hadden een conversie van de laparoscopische procedure nodig: drie laparotomieën (bij 2 patiënten vanwege bloeding en bij een patiënt vanwege onvoldoende blootstelling door obesitas) en één handmatig geassisteerde procedure (vanwege extreme obesitas). Na een gemiddelde follow-up van 47 maanden vertoonde een patiënt een relaps.

Zenuwsparende laparoscopische retroperitoneale lymfeklierdissectie wordt al meer dan tien jaar gebruikt bij de behandeling van testiskanker in stadium I/II. Het UMCG was een van de eerste testiskankercentra wereldwijd die deze techniek introduceerde voor adjuvante behandeling van testiskanker in verder gevorderde stadia, bijvoorbeeld laparoscopische resectie van retroperitoneale restziekte na cisplatine-combinatiechemotherapie bij NSTGCT's. In de jaren daarna groeide de laparoscopische serie uit tot 75 patiënten, een van de grootste laparoscopieseries in de huidige literatuur met betrekking tot resectie van retroperitoneale restziekte bij NSTGCT's na cisplatine-combinatiechemotherapie. In **Hoofdstuk 5** wordt een serie van 150 patiënten beschreven met retroperitoneale restziekte na afronding van chemotherapie; resultaten van 75 patiënten die adjuvante laparoscopische chirurgie (L-RRRTM) ondergingen werden vergeleken met een groep van 75 retrospectief geselecteerde patiënten die conventionele mediane laparotomie ondergingen. L-RRRTM werd primair gepland bij 89 patiënten met een gemiddelde restmassa diameter van 20 (bereik 5-70) mm; conversie was echter nodig bij 14 patiënten (15%). Perioperatieve complicaties kwamen zowel voor in de L-RRRTM-groep als in de conventionele RRRTM (C-RRRTM)-groep. Zoals verwacht kon worden was de gemiddelde duur van een C-RRRTM langer dan de operatieve tijd bij een L-RRRTM (gemiddeld 221 versus 146 minuten, p <.001). In de L-RRRTM-groep hadden 9/75 patiënten (12%) postoperatieve complicaties versus 26/75 patiënten in de C-RRRTM-groep (inclusief conversies) (35%,p <.001). Gemiddeld postoperatief verblijf in de L-RRRTM-groep was significant korter dan in de C-RRRTM-groep (gemiddeld 1 dag vs. 5 dagen, p <.001). Er werd een gemiddelde follow-up tijd bereikt van 79 (2-144) maanden. In deze periode beleefden 4 (5%) patiënten in de L-RRRTM-groep een relaps versus 23 (31%) in de C-RRRTM-groep (p <.001). Aangezien de opzet van deze studie louter descriptief is, is het moeilijk de twee soorten modaliteiten van resectie te vergelijken. Wel kan worden geconcludeerd dat de laparoscopische procedure bruikbaar is en ook oncologisch veilig lijkt bij geselecteerde patiënten, en resulteert in korter ziekenhuisverblijf en goede oncologische en uitstekende kosmetische resultaten. Langetermijn follow-up is voorzien bij een groot cohort patiënten. Met toenemende ervaring over de jaren heen kunnen we zeggen dat bij de selectie van patiënten voor L-RRRTM andere factoren een rol spelen dan enkel de omvang van de tumor. Deze criteria zijn dynamisch; afhankelijk van enerzijds de zich ontwikkelende skills van de chirurg oncologen en anderzijds de anatomische locatie van de retroperitoneale restmassa, die per geval wordt geëvalueerd. Een eventueel benodigde conversie hoeft voor de patiënt niet als 'complicatie' te worden beschouwd. Gezien de voordelen van een minimaal invasieve procedure kan de patiënt, vooropgesteld dat er solide argumenten en ervaringen zijn voor deze mogelijkheid, beter een laparoscopische procedure worden aangeboden dan een conventionele laparotomie. Na een geslaagde laparoscopie verlaat de jonge testiskankerpatiënt het ziekenhuis met drie nauwelijks zichtbare littekens. Geen litteken in het midden dat als een permanente chirurgische tatoeage aan de ondergane testiskankerbehandeling herinnert. Verdere uitkomstgegevens op de lange termijn moeten worden afgewacht.

De discussie over minimaal invasieve procedures wordt altijd vertroebeld door controverses rond de zorg van patiënten met uitgezaaide non-seminomateuze testiskiemceltumoren met het oog op de uitgebreidheid van resectie. In de VS bestaat in de urologie een sterke chirurgische traditie die de behandeling richting een meer agressieve chirurgische aanpak stuurt, terwijl in Europa over het algemeen de voorkeur wordt gegeven aan een meer conservatieve chirurgische aanpak, waarbij alleen de 'zichtbare restmassa' wordt verwijderd. Deze discussie rond de optimale chirurgische behandeling van postchemotherapeutische retroperitoneale restmassa wordt verhevigd door het gebrek aan vergelijkende en gerandomiseerde gegevens, en wordt beïnvloed door geografisch verschillende chirurgische keuzes bij de behandeling van patiënten met NSTGCT's in een gevorderd stadium. Bovendien zijn de resultaten van de studie die wordt gepresenteerd in **Hoofdstuk 5** gebaseerd op de Nederlandse en Europese richtlijnen voor behandeling van testiskanker, waarbij enkel de retroperitoneale restziekte wordt verwijderd om de vitale resttumor en teratomen te verwijderen en zo een groeiend teratoomsyndroom en de ontwikkeling van kwaadaardige niet-kiemceltumoren te voorkomen. Deze aanpak heeft uitstekende overlevingsratio's van meer dan 80-90%. Ook zijn de principes van resectie in de laparoscopische adjuvante oncologische chirurgische aanpak bij de gecombineerde behandeling van non-seminomateuze testiskanker in een gevorderd stadium gelijk aan die van conventionele chirurgie voor uitgezaaide testiskanker.

In **Hoofdstuk 6** wordt een nieuwe aanpak voor verwijdering van restmassa in non-seminomateuze kiemceltumoren beschreven. Deze aanpak kan worden gevolgd bij een subgroep van patiënten met niet-gereseceerde ziekte of een recidief in het retroperitoneum in de postchemotherapeutische chirurgische setting na eerdere retroperitoneale lymfeklierdissectie (RPLND) of RRRTM. Met het vertrouwen en de ervaring geput uit bijnier chirurgie werd de Posterior Retroperitoneoscopic Resection (PRR) uitgevoerd bij een patiënt met non-seminomateuze kiemceltumorrelaps gelokaliseerd in de linker retrocrurale ruimte. Postoperatief herstel verliep voorspoedig en het ziekenhuisverblijf duurde een dag. Hersteloperaties gaan gepaard met significante morbiditeit en risico's, en zijn vaak technisch uitdagende procedures vanwege postchemotherapeutische desmoplastische reactie, vernietigde weefsellagen en ernstige verklevingen vanwege een eerdere operatie. Deze nieuwe aanpak, de PRR, kan daarom worden overwogen bij het vaststellen van een behandelplan voor individuele patiënten. Hoewel het niet vaak nodig zal zijn, zou het zeker deel moeten uitmaken van het palet van chirurgische keuzes die kunnen worden gemaakt bij patiënten met testiskanker met restziekte (recidief) na eerdere combinatiechemotherapie behandeling.

Het UMCG, een tertiair verwijscentrum voor patiënten met testiskanker, heeft al veel institutioneel onderzoek gepubliceerd over dit onderwerp, waarin uiteenlopende aspecten van testiskanker worden behandeld. Dit proefschrift is een van vele in deze uitvoerige onderzoekstraditie. Om inzicht te verschaffen in deze specifieke academische geschiedenis is een **Appendix** toegevoegd aan dit proefschrift. In dit toegevoegde hoofdstuk wordt een gedetailleerd historisch overzicht geschetst van de behandeling van testiskanker aan het UMCG zoals dit is uitgevoerd door de afdeling Chirurgische Oncologie vanaf de jaren zestig van de vorige eeuw tot aan nu, met chirurgische en niet-chirurgische behandelmodaliteiten. Ook de transformatie in de behandeling van testiskanker in de afgelopen tientallen jaren tot een multimodaliteiten behandeling waarin tegenwoordig meer dan acht medische disciplines (chirurgen, urologen, medisch oncologen, stralingsoncologen, pathologen, radiologen, nucleair geneeskundigen, genetici, psychologen) en basisonderzoekers betrokken zijn, wordt beschreven.

Appendix: Historical Overview of Testicular Cancer Treatment at the UMCG

Appendix

Previously, in the introduction of this thesis, an overview was presented about today's epidemiology, etiology, pathology, metastatic pattern, symptomatology, diagnostics, staging and (combined) treatment of testicular cancer and its prognosis. In this historical overview a short history of the treatment of testicular cancer is given as it was performed at the Department of Surgical Oncology from the sixties of the last century till now and how the testicular cancer treatment shifted to a multimodality treatment in which today over eight medical disciplines (surgeons, urologists, medical oncologists, radiation oncologists, pathologists, radiologists, nuclear medicine physicians, geneticist, psychologists) and basic researchers are involved.

Testicular cancer was one of the first tumor types for which in 1971 in the Netherlands a national study group, 'Commissie voor Testis Tumoren' was established. The intention was to uniform the treatment and to give advice when necessary. Few years later (1978) the national guideline 'Protocol Testistumoren' was developed with the support of the Dutch Cancer Society (Koningin Wilhelmina Fonds, de Nederlandse Organisatie voor de Kankerbestrijding (KWF-NOK)). The goal of this guideline was to achieve uniformity in the histopathological classification of seminomatous and nonseminomatous testicular germ cell tumors, to stimulate staging according to the TNM-classification, to describe operative procedures for inguinal orchiectomy and bilateral retroperitoneal lymph node dissection, to give radiation guidelines, as well as to advice on the follow-up after treatment. Moreover the idea was to start a registration of patients with a malignant testicular tumor[1].

Since the early sixties testicular cancer is one of the clinical treatment and research topics within the Department of Surgical Oncology of the former 'Algemeen Provinciaal, Stads- en Academisch Ziekenhuis (APSAZ)', later called Academisch Ziekenhuis Groningen (AZG) and today University Medical Center Groningen (UMCG). Since that time all patients with a suspicious testicular tumor underwent an inguinal orchiectomy. In those days, a centralized histopathology review was performed at the Antoni van Leeuwenhoekziekenhuis in Amsterdam. After a definitive histological diagnosis, patients were staged with an intravenous pyelogram, bipedal lymphography, chest X-ray and tomography of the lungs[2]. In case of suspected retroperitoneal metastatic disease, a supraclavicular lymph node biopsy was performed. When supraclavicular nodal disease was encountered, the patient was considered to have distant lymphogenous disease and surgically 'incurable'. Patients were initially staged according to the system of Skinner and Scardino (Table 1a), after 1979 according to the Royal Marsden classification

developed by Peckham (Table 1b)[3,4]. In 1997 was the International Germ Cell Consensus Classification (IGCCCG) introduced, a prognostic factor-based staging system for metastatic germ cell cancers, classifying the nonseminomatous tumors in good, intermediate, and poor prognosis[5].

Table 1a.
Staging system by Skinner and Scardino

Stage	I	Tumor confined to the scrotum, negative nodes and no other evidence of disease
Stage	IIA	Metastases fewer than 6 retroperitoneal lymph nodes, with no nodes >2 cm in diameter
Stage	IIB	Metastases to 6 or more retroperitoneal lymph nodes or any metastasis >2 cm in diameter or extra-capsular spread
Stage	IIC	Bulky abdominal disease detected grossly on abdominal examination before operation, usually associated with significant ureteral deviation and/or obstruction
Stage	III	Metastases above the diaphragm or to the viscera

Table 1b.
Staging for testicular tumors by Peckham

Stage	I	Tumor limited to the testis
Stage	II	Metastases confined to abdominal lymph nodes
	IIA	Metastases <2 cm
	IIB	Metastases 2-5 cm
	IIC	Metastases >5 cm
Stage	III	Involvement of supradiaphragmatic and infradiaphragmatic lymph nodes. Abdominal status as for Stage II
Stage	IV	Extra lymphatic metastases. Abdominal status as for Stage II, 0 for negative nodes.
Stage	IV	Lung status: • L1: ≤3 metastases, ≤2 cm in diameter • L2: multiple, ≤2 cm in diameter • L3: multiple, >2 cm in diameter

Table 1a and 1b: Formerly used staging systems in TGCT[3,4].

In the early days patients with a nonseminomatous tumor were treated by the Department of Surgical Oncology and with a seminomatous tumor by the Department of Radiation Oncology. Today however treatment has shifted to a multimodality treatment in which the Departments of Surgical Oncology, Urology, Medical Oncology and Radiation Oncology are involved and patients with seminomas as well as nonseminomas are discussed in the weekly Multidisciplinary Cancer Conferences (MCCs).

The transabdominal bilateral retroperitoneal lymph node dissection for nonseminomatous germ cell tumors of the testis was introduced in the APSAZ by Oldhoff in 1963[6]. The dissection extends from the renal vessels cranially to the external iliac arteries caudally. The transabdominal approach was given preference over the thoraco-abdominal procedure because the transabdominal approach provided sufficient access and the opportunity to remove lymph nodes adequately on both sides. Between 1963-1968, stage I and II patients underwent this procedure as the only treatment after orchiectomy. In clinical stage I patients, no tumor was encountered in the removed retroperitoneal nodes in 80% of the patients and in the remaining 20% of these patients the retroperitoneal lymph node dissection was considered not only as diagnostic but also as a therapeutic procedure. Clinical stage II patients underwent an exploratory laparotomy and, when possible, a bilateral retroperitoneal lymph node dissection[7]. If (sporadically) patients presented with inguinal nodal disease also an inguinal lymph node dissection was performed. In contrast to this pure surgical treatment at the same time testicular cancer patients in other centers in the Netherlands were generally treated with radiation of the retroperitoneal nodal area and/or mediastinum[7,8].

In Groningen the treatment of nonseminomatous testicular cancer changed in 1968 after the successful reports in literature of adjuvant chemotherapy with actinomycine-D[6]. In case of histopathologic documentation of retroperitoneal disease after transabdominal bilateral retroperitoneal lymph node dissection, adjuvant chemotherapy was administered consisting of 1 mg actinomycine-D per day in an 8 hours continuous intravenous infusion during 5 days, every 6 weeks over a period of 2-years, sometimes combined with radiation treatment. In those days this chemotherapy was given by the surgical oncologists themselves. When the retroperitoneal disease was primarily considered irresectable, patients were treated with an induction course consisting of 3-courses of actinomycine-D followed by a second laparotomy and, if possible, resection of the residual retroperitoneal disease, followed again by adjuvant actinomycine-D treatment[8]. The 3-years survival for stage I disease was 90% and for stage IIA and IIB 70%. Survival for stage IIC and stage III was disappointing with 3-years survival of only 25%[8-10].

At the end of the seventies there were three new developments in the treatment of testicular cancer: 1) the testicular tumor markers, alpha-fetoprotein (AFP), betachoriongonadotropin (B-HCG), and lactate dehydrogenase (LDH) were introduced in the diagnosis of testicular cancer and later on in the staging and evaluation of testicular cancer treatment; 2) Computed Tomography (CT) of the abdomen and chest was introduced in the staging of testicular cancer and quickly replaced the previous described staging methods, intravenous pyelogram, bipedal lymphography and tomography of the lungs; 3) discovery of cisplatin and the introduction of the cisplatin based combination chemotherapy by Einhorn with cisplatin, vinblastin and bleomycin (PVB) for disseminated testicular cancer[10]. Prolonged remissions were achieved in 70% of the disseminated testicular cancer patients treated with PVB[10]. In the Netherlands, including Groningen, shortly after the same survival figures were published[11].

With the introduction of PVB in Groningen, the treatment of testicular cancer became a team approach of pathologist, surgical oncologist, medical oncologist, radiologist and anesthesiologist. All new and treated patients with a nonseminomatous tumor were discussed within the weekly MCC. The medical oncologists had to 'learn' how to deliver 'safely' the cisplatin based combination chemotherapy[12-14]. The radiologist had to learn how to 'assess' the post chemotherapy retroperitoneal CT scans in particular with respect to tumor response. The surgical oncologists faced the resection of fibrosed and/or necrotic residual disease. The anesthesiologist had to learn how to deal with the side effects of bleomycin to the pulmonary tissue during general anesthesia[14]. The pathologist had to evaluate the resected tumor tissue, e.g. necrosis, fibrosis, mature teratoma and/or viable germ cell cancer. Two research questions were extensively studied 1) tumor maturation due to chemotherapy and 2) immune histochemical analysis of tumor marker production by different histological components of nonseminomatous germ cell tumors[15].

The cisplatin based combination chemotherapy treatment of metastatic nonseminomatous testicular cancer suddenly brought together a range of medical specialists and researchers from different medical disciplines and the testicular research line expanded successfully within the 'Facultaire Onderzoeksprogramma Oncologie' of the Medical Faculty of the Groningen University.

Schraffordt Koops and Sleijfer successfully introduced the 'wait and see' policy in the APSAZ for stage I disease and exploratory laparotomies were no longer performed[16,17]. In case of a recurrence, effective chemotherapy was available[18]. Treatment of disseminated nonseminomatous tumors consisted of cisplatin, vinblastin and bleomycin (PVB) and since the mid-eighties of bleomycin, etoposide and cisplatin (BEP). More recently the systemic treatment is based on so called 'IGCCCG prognostic factors' and individualized for example in patients with pulmonary disease, administering 4 cycles EP instead of 3 cycles BEP[5]. After systemic chemotherapy there might be a biochemical complete response, with or without residual retroperitoneal and/or lung disease evaluated on abdominal/chest CT. All residual retroperitoneal/lung disease needs to be resected[19-21]. Further treatment is depending on the histopathology of the resected specimen. In case of necrosis or mature teratoma no further therapy is indicated, while second line chemotherapy might be indicated when viable germ cell cancer is encountered.

Also the treatment of seminomatous tumors of the testis changed and improved during the last two decades, mainly due to CT radiation planning, less radiation doses and the introduction of systemic chemotherapy for stage III and IV disease. More recently treatment for stage I disease has changed: wait and see policy is implemented, one course of carboplatin or still radiation. Orchiectomy is the only surgical part of the treatment for patients with a seminoma of the testis. Further treatment, radiation or systemic treatment, is based on the disease stage and the advisement of the multidisciplinary cancer conference (MCC).

In Groningen, the modified retroperitoneal lymph node dissection was introduced: only resection of residual retroperitoneal disease with the ultimate goal to reduce the morbidity of retrograde ejaculation[22,23]. For an adequate vascular access to continuously deliver PVB, in the early eighties patients received an AV-fistula between the radial artery and the cephalic vein[23]. The complication rate of this surgical procedure was high and therefore the Venous Access Port (VAP) was successfully introduced in the mid-eighties[25].

In Europe, there are European Society of Medical Oncology (ESMO) guidelines with regard to the treatment of disseminated nonseminomatous tumors but these do not fully correspond with the guidelines of the National Comprehensive Cancer Network (NCCN)[26,27]. In contrast to the small differences in systemic treatment, differences are very large with respect to the surgical removal of residual retroperitoneal tumor mass(es). At the UMCG only the macroscopic residual abnormalities are removed, while in the USA complete or modified (template) retroperitoneal lymph node dissections are still performed[19-21,26,27]. One of the advantages of the UMCG strategy was the less sexual disorder[28-30].

At the UMCG, resection of residual retroperitoneal disease is centralized, in contrast to other centers in the West where the referring general surgeon or urologist generally performs the adjuvant surgery. The role of surgery in the treatment of disseminated testicular cancer was well defined at the end of the nineties, as well as all surgical research questions seemed to be answered. Therefore the research within the Department of Surgical Oncology, in close collaboration with the Department of Medical Oncology shifted towards the Department of Genetics and the Department of Psychosocial Oncology on subjects such as genetic

susceptibility, tumor biology, endocrine aspects, sexuality, quality of life, survivorship issues and long-term toxicity in testicular cancer[31-45]. The last decade Gietema of the Department of Medical Oncology has especially focused on long-term effects of testicular cancer treatment within national and international collaborative groups[46-48].

With the extensive achieved experience in laparoscopic surgery, this minimal invasive operative technique was introduced by Hoekstra a decade ago in the treatment of testicular cancer at the UMCG. In most centers laparoscopy is used as a minimal invasive staging procedure, e.g. nerve preserving uni- or bilateral retroperitoneal lymph node dissection (RPLND), for stage I NSTGCTs. At the UMCG the surgical staging, RPLND or exploratory laparotomy, was already abandoned in the mid-eighties when the CT staging became available. The technique of laparoscopy was for the first time used at the UMCG in the resection of residual retroperitoneal tumor mass (RRRTM) in 2004. Since then performing laparoscopic resections of RRRTMs in testicular cancer patients has become a routine procedure at the UMCG for the surgical oncologists.

Although the technique of laparoscopic resection of RRTMs is safe, this minimally invasive procedure, with a nice oncological and cosmetic outcome, is still not widely accepted in the Netherlands, Europe and the United States[49,50].

Are there still new surgical treatment options in the treatment of testicular cancer? With the availability of the Da Vinci Robot at the UMCG in 2018, the technique of robotic (assisted) resection of residual retroperitoneal tumor masses will be explored in the nearby future in the treatment of disseminated testicular cancer with the goal to resect residual retroperitoneal tumor masses with the same cosmetic result but less morbidity, e.g. preserving sexual function.

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10

Dankwoord
Curriculum Vitae
Publicaties

Dankwoord

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Curriculum Vitae

Çiğdem Öztürk werd geboren op 15 mei 1981 te ‘s Gravenhage. Zij is de dochter van Ramazan Öztürk en Hava Soysal en de zus van Renan Anıl. In 1999 behaalde zij het Atheneum-diploma aan het Thomas More College te ’s Gravenhage. Aangezien zij werd uitgeloot voor de studie Geneeskunde, volgde zij eerst de studie Psychologie aan de Universiteit van Leiden. In 2001 jaar kon zij starten met de studie Geneeskunde in het Leids Universitair Medisch Centrum. Op 27 maart 2008 legde zij het artsexamen succesvol af. Datzelfde jaar studeerde zij ook af in de Klinische en Gezondheidspsychologie.

In 2008 startte zij als arts-assistent op de afdeling Heelkunde van het Amphia Ziekenhuis in Breda. In 2009 ging zij in het Universitair Medisch Centrum in Groningen werken als arts-assistent chirurgie en een jaar later als arts-onderzoeker. In deze periode werd de basis voor het proefschrift gelegd, onder leiding van Prof. dr. H.J. Hoekstra. In 2011 werd zij geselecteerd voor de opleiding Heelkunde in de Regio Groningen (opleider Prof dr. H.J. ten Duis). Van 2011 tot 2014 werd de chirurgische opleiding in het Ziekenhuis Groep Twente te Almelo doorlopen (opleider Dr. J.G. van Baal), waarna in september 2014 de opleiding werd vervolgd in het Universitair Medisch Centrum in Groningen (opleider Prof dr. E. Heineman). Zij heeft gekozen voor de differentiatie gastro-intestinale chirurgie. De opleiding Heelkunde en hiermee ook haar differentiatie werd afgerond in het Medisch Centrum Leeuwarden (opleider Drs. M. Emous).

Per 1 oktober 2018 is Çiğdem werkzaam in het Zuyderland Ziekenhuis in Limburg als fellow Chirurgische Oncologie. Çiğdem is getrouwd met Ehsan Baharvand en hun zoon Kiyan werd geboren op 12 oktober 2016.

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